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FILE 'HCAPLUS' ENTERED AT 21:17:00 ON 23 DEC 2003
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FILE 'USPATFULL' ENTERED AT 21:17:00 ON 23 DEC 2003
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=> s l3
L4          84 L3

=> s l4 and lung(p)(cancer? or tumor? or tumour? or neoplas?)
L5          31 L4 AND LUNG(P)(CANCER? OR TUMOR? OR TUMOUR? OR NEOPLAS?)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6          30 DUP REM L5 (1 DUPLICATE REMOVED)

=> s l6 and radiat?
L7          5 L6 AND RADIAT?

=> d l7 abs ibib kwic hitstr 1-5

L7   ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2003 ACS on STN
AB   Methods are provided to treat neoplasia disorders in a mammal using a
     combination of radiation and a matrix metalloproteinase
     inhibitor.
ACCESSION NUMBER:         2000:456914  HCAPLUS
DOCUMENT NUMBER:          133:68928
TITLE:                    Method of using a matrix metalloproteinase inhibitor
                          and radiation therapy as combination therapy
                          in the treatment of neoplasia
INVENTOR(S):              McKearn, John P.; Gordon, Gary; Cunningham, James J.;
                          Gately, Stephen T.; Koki, Alane T.; Masferrer, Jaime
                          L.
PATENT ASSIGNEE(S):       G.D. Searle & Co., USA
SOURCE:                   PCT Int. Appl., 125 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   17
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2000038717      A2   20000706       WO 1999-US30676  19991222
     WO 2000038717      A3   20010201
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2356459         AA   20000706       CA 1999-2356459  19991222
     EP 1140178         A2   20011010       EP 1999-966587   19991222
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002533405	T2	20021008	JP 2000-590668		19991222
ZA 2001005055	A	20020920	ZA 2001-5055		20010620
ZA 2001005120	A	20020107	ZA 2001-5120		20010621
PRIORITY APPLN. INFO.:			US 1998-113786P	P	19981223
			WO 1999-US30676	W	19991222

TI Method of using a matrix metalloproteinase inhibitor and **radiation** therapy as combination therapy in the treatment of neoplasia

AB Methods are provided to treat neoplasia disorders in a mammal using a combination of **radiation** and a matrix metalloproteinase inhibitor.

IT Antitumor agents
(bladder carcinoma; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Bladder
Bladder
(carcinoma, inhibitors; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Uterus, neoplasm
Uterus, neoplasm
(cervix, inhibitors; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Antitumor agents
(cervix; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Antitumor agents
(digestive tract; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Antitumor agents
(head; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT **Lung, neoplasm**
Lung, neoplasm
(inhibitors; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of **neoplasia**)

IT Antitumor agents
Antitumor agents
(**lung**; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of **neoplasia**
)

IT Antitumor agents
(mammary gland; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Antitumor agents
Radiotherapy
(matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Antitumor agents
(neck; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT Digestive tract
Digestive tract
Head
Head
Mammary gland
Mammary gland
Neck, anatomical
Neck, anatomical

(neoplasm, inhibitors; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT **192329-42-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AG 3340; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

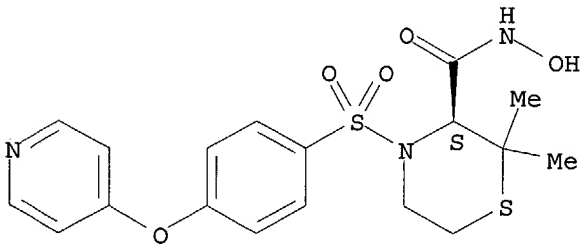
IT 15866-90-7, CMT-3 154039-60-8, Marimastat 179545-77-8, Bay-12-9566 191537-76-5, D 2163 226388-60-9 226388-66-5 226389-91-9 226395-57-9 226395-66-0 226395-67-1 226395-68-2 226395-93-3 226396-02-7 226396-03-8 226396-26-5 279221-20-4 279221-21-5 279221-22-6 279221-23-7 279221-25-9 279221-26-0 279221-27-1 279221-28-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

IT **192329-42-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AG 3340; matrix metalloproteinase inhibitor and **radiation** therapy combination in treatment of neoplasia)

RN 192329-42-3 HCAPLUS
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 2 OF 5 USPATFULL on STN
AB The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of **radiation** therapy and a cyclooxygenase-2 inhibitor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:302884 USPATFULL
TITLE:	Combination therapy of **radiation** and a COX-2 inhibitor for treatment of neoplasia
INVENTOR(S):	McKearn, John P, St. Louis, MO, United States Masferrer, Jaime L, Ballwin, MO, United States Milas, Luka, Houston, TX, United States

PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6649645	B1	20031118	
APPLICATION INFO.:	US 1999-385214		19990827	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-113786P	19981223	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Criares, Theodore J.
ASSISTANT EXAMINER: Kim, Jennifer
LEGAL REPRESENTATIVE: Bulock, Joseph W., Warner, James M.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 1434
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Combination therapy of **radiation** and a COX-2 inhibitor for treatment of neoplasia

AB The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of **radiation** therapy and a cyclooxygenase-2 inhibitor.

SUMM The present invention relates to a combination of **radiation** therapy and a cyclooxygenase-2 (COX-2) inhibitor for treatment of neoplasia disorders. More specifically, this invention relates to the use of COX-2 inhibitors in combination with **radiation** therapy for treating cancer.

SUMM . . . molecular level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or **radiation**, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene". Suppressive genes are growth regulatory genes, which. . .

SUMM Cancer is now primarily treated with one or a combination of three types of therapies: surgery, **radiation**, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at. . .

SUMM Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of breast, **lung**, and testicular **cancer**.

SUMM . . . adverse side effects include cytopenia, infection, cachexia, mucositis in patients receiving high doses of chemotherapy with bone marrow rescue or **radiation** therapy; alopecia (hair loss); cutaneous complications such as pruritis, urticaria, and angioedema; neurological complications; pulmonary and cardiac complications in patients receiving **radiation** or chemotherapy; and reproductive and endocrine complications (M. Abeloff, et al., Alopecia and Cutaneous Complications, in Clinical Oncology 755-56 (Abeloff,. . .

SUMM In general, **radiation** therapy is employed as potentially curative therapy for patients who present with clinically localized disease and are expected to live. . .

SUMM . . . of newly diagnosed prostate cancer patients fall into this category. Approximately 10% of these patients (7% of total patients) undergo **radiation** therapy. Approximately 80% of patients who have undergone **radiation** as their primary therapy have disease persistence or develop recurrence or metastasis within five years after

treatment. Currently, most of. . .

SUMM The adverse side effects induced by chemotherapeutic agents and **radiation** therapy have become of major importance to the clinical management of cancer patients.

SUMM Current therapies for prostate cancer focus upon reducing levels of dihydrotestosterone to decrease or prevent growth of prostate cancer. **Radiation** alone or in combination with surgery and/or chemotherapeutic agents is often used.

SUMM . . . 90, 1609-20). They are also involved in the response of tumor and normal tissues to cytotoxic agents such as ionizing **radiation** (Milas and Hanson, Eur. J. Cancer 1995, 31A, 1580-5). Prostaglandin production is mediated by two cyclooxygenase enzymes: COX-1 and COX-2.. . .

SUMM . . . of such response. Prostaglandin E.sub.2, and prostaglandin I.sub.2 protect jejunum crypt cells, and prostaglandin I.sub.2 protects B16 melanoma cells from **radiation** damage. Inhibition of prostaglandin synthesis also induces an accumulation of cells in the G.sub.2+M phases of the cell cycle, which are generally considered to be the most sensitive to ionizing **radiation**. With the inhibition of prostaglandin synthesis, prostaglandin-induced immunosuppressive activity was diminished and antitumor immunologic responses were able to potentiate tumor response to **radiation**. Finally, prostaglandins are vasoactive agents and are thus likely to regulate tumor blood flow and perfusion.

SUMM . . . tumor cure rate in mice after radiotherapy (Milas et al., Cancer Res. 1990, 50, 4473-7). The influence of oxyphenylbutazone and **radiation** therapy on cervical cancer has been studied. (Weppelmann and Monkemeier, Gyn. Onc., 1984, 47, 196-9).

SUMM Antiangiogenesis therapy has been used as an adjunct to chemotherapy, **radiation** therapy, or surgery. (Kumar and Armstrong, Emerging Drugs 1997, 2, 175-190). Recently, it was reported that the combination of **radiation** with antiangiogenic compounds produces an additive effect on the growth of human tumor xenografts (Gorski et al., Cancer Res. 1998;. . .

SUMM . . . 40, 396). COX-2 specific inhibitors prevent angiogenesis in experimental animals, but their efficacy in enhancing in vivo tumor response to **radiation** has not been established.

DRWD FIG. 3 shows the effect of a COX-2 inhibitor on dose-dependent and **radiation**-induced delay in tumor growth.

DRWD FIG. 4 shows the effect of a COX-2 inhibitor on tumor cure by **radiation**.

DETD Treatment of a neoplasia disorder in a mammal in need of such treatment is provided by methods and combinations using **radiation** and a COX-2 inhibitor. The method comprises treating a mammal with a therapeutically effective amount of a combination comprising a. . .

DETD Specific inhibitors of COX-2 potentiate tumor response to **radiation**. Thus, COX-2 inhibitors improve the efficacy of radiotherapy.

DETD In one embodiment of the invention a method for treating **neoplasia** in a subject in need of such treatment comprises treating the subject with **radiation** therapy and a therapeutically effective amount of a cyclooxygenase-2 inhibitor or pharmaceutically acceptable salt or derivative thereof wherein the **neoplasia** is selected from **lung cancer**, breast **cancer**, gastrointestinal **cancer**, bladder **cancer**, head and neck **cancer**, and cervical **cancer**.

DETD The methods and compositions of the present invention provide one or more benefits. A combination of a COX-2 inhibitor with **radiation**

therapy of the present invention are useful in treating neoplasia disorders. Preferably, the COX-2 inhibitor agent or agents and the **radiation** therapies of the present invention are administered in combination at a low dose, that is, at a dose lower than. . .

DETD A benefit of lowering the dose of the **radiation** therapies of the present invention administered to a mammal includes a decrease in the incidence of adverse effects associated with. . .

DETD The phrases "low dose" or "low dose amount", in characterizing a therapeutically effective amount of the COX-2 inhibitor and the **radiation** or therapy in the combination therapy, defines a quantity of such therapy, or a range of quantity of such therapy, that is capable of diminishing the neoplastic disease while reducing or avoiding one or more **radiation**-induced side effects, such as myelosupression, cardiac toxicity, skin erythema and desquamation, alopecia, inflammation or fibrosis.

DETD The phrase a "radiotherapeutic agent" refers to the use of electromagnetic or particulate **radiation** in the treatment of neoplasia. Examples of radiotherapeutic agents are provided in, but not limited to, **radiation** therapy and is known in the art (Hellman, Principles of **Radiation** Therapy, Cancer, in Principles and Practice of Oncology, 248-75 (Devita et al., ed., 4th edit., volume 1, 1993).

DETD For patients who initially present without advanced or metastatic cancer, a COX-2 inhibitor in combination with **radiation** therapy, is used as a continuous post-treatment therapy in patients at risk for recurrence or metastasis (for example, in adenocarcinoma. . .

DETD For patients who initially present with advanced or metastatic cancer, a COX-2 inhibitor in combination with **radiation** therapy of the present invention is used as a continuous supplement to, or possible replacement for hormonal ablation. The goal. . .

DETD . . . regimen of one or more chemotherapeutic agents, cycled over a one year time period. In the treatment of colorectal cancer, **radiation** alone or in combination with surgery and/or chemotherapeutic agents is often used. Preferred chemotherapeutic agents include fluorouracil, and Levamisole. Preferably,. . .

DETD Current therapies for prostate cancer focus upon reducing levels of dihydrotestosterone to decrease or prevent growth of prostate cancer. **Radiation** alone or in combination with surgery and/or chemotherapeutic agents is often used.

DETD . . . obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant **radiation**; and chemotherapy. For the treatment of metastatic adenocarcinoma, the preferred chemotherapy consists of 5-fluorouracil, followed weekly cisplatin therapy.

DETD **Lung Cancer**

DETD In many countries including Japan, Europe and America, the number of patients with **lung cancer** is fairly large and continues to increase year after year and is the most frequent cause of **cancer** death in both men and women. Although there are many potential causes for **lung cancer**, tobacco use, and particularly cigarette smoking, is the most important. Additionally, etiologic factors such as exposure to asbestos, especially in. . . identified as an important factor. Finally, genetic factors have also been identified as another factor that increase the risk of **cancer**.

DETD **Lung cancers** can be histologically classified into non-small cell **lung cancers** (e.g. squamous cell carcinoma (epidermoid), adenocarcinoma, large cell carcinoma (large cell

anaplastic), etc.) and small cell **lung cancer** (oat cell). Non-small cell **lung cancer** (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell **lung cancer** (SCLC). Thus, chemotherapeutic formulas and **radiation** therapy are different between these two types of **lung cancer**.

DETD Non-Small Cell **Lung Cancer**

DETD Where the location of the non-small cell **lung cancer** **tumor** can be easily excised (stage I and II disease) surgery is the first line of therapy and offers a relatively good chance for a cure. However, in more advanced disease (stage IIIa and greater), where the **tumor** has extended to tissue beyond the bronchopulmonary lymph nodes, surgery may not lead to complete excision of the **tumor**. In such cases, the patient's chance for a cure by surgery alone is greatly diminished. Where surgery will not provide complete removal of the NSCLC **tumor**, other types of therapies must be utilized.

DETD Today **radiation** therapy is the standard treatment to control unresectable or inoperable NSCLC. Improved results have been seen when **radiation** therapy has been combined with chemotherapy, but gains have been modest and the search continues for improved methods of combining. . .

DETD **Radiation** therapy is based on the principle that high-dose **radiation** delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The **radiation** dosage regimen is generally defined in terms of **radiation** absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of **radiation** a patient receives will depend on various consideration but the two most important considerations are the location of the tumor. . . the body, and the extent to which the tumor has spread. A prefered course of treatment for a patient undergoing **radiation** therapy for NSCLC will be a treatment schedule over a 5 to 6 week period, with a total dose of. . .

DETD However, as NSCLC is a systemic disease, and **radiation** therapy is a local modality, **radiation** therapy as a single line of therapy is unlikely to provide a cure for NSCLC, at least for those tumors that have metastasized distantly outside the zone of treatment. Thus, the use of **radiation** therapy with other modality regimens have important beneficial effects for the treatment of NSCLC.

DETD Generally, **radiation** therapy has been combined temporally with chemotherapy to improve the outcome of treatment. There are various terms to describe the temporal relationship of administering **radiation** therapy and chemotherapy, and the following examples are the preferred treatment regimens and are generally known by those skilled in. . . the art and are provided for illustration only and are not intended to limit the use of other combinations. "Sequential" **radiation** therapy and chemotherapy refers to the administration of chemotherapy and **radiation** therapy separately in time in order to allow the separate administration of either chemotherapy or **radiation** therapy. "Concomitant" **radiation** therapy and chemotherapy refers to the administration of chemotherapy and **radiation** therapy on the same day. Finally, "alternating" **radiation** therapy and chemotherapy refers to the administration of **radiation** therapy on the days in which chemotherapy would not have been administered if it was given alone.

DETD It is reported that advanced non-small cell **lung** **cancers** do not respond favorably to single-agent chemotherapy and useful therapies for advanced inoperable **cancers** have been

limited. (J. Clin. Oncol. 1992, 10, 829-838).

DETD . . . macrolide antibiotics as a drug delivery carrier capable of transporting anthoracycline-type anticancer drugs into the lungs for the treatment of **lung cancers**. However, the macrolide antibiotics specified herein are disclosed to be only a drug carrier, and there is no reference to the therapeutic use of macrolides against non-small cell **lung cancers**.

DETD WO 93/18652 refers to the effectiveness of the specified 16-membered-ring macrolides such as bafilomycin, etc. in treating non-small cell **lung cancers**, but they have not yet been clinically practicable.

DETD . . . which contribute to host immune responses, but there is no reference to the effect of this drug on non-small cell **lung cancers**.

DETD . . . of antimicrobial drugs can be used as an anticancer agent, but does not refer to their application to non-small cell **lung cancers**.

DETD . . . addition, interleukins are known to have an antitumor effect, but have not been reported to be effective against non-small cell **lung cancers**.

DETD Any 14- or 15-membered-ring macrolides have not been reported to be effective against non-small cell **lung cancers**.

DETD Small Cell **Lung Cancer**

DETD Approximately 15 to 20 percent of all cases of **lung cancer** reported worldwide is small cell **lung cancer** (SCLC). (Ihde, **Cancer** 1984, 54, 2722). Currently, treatment of SCLC incorporates multi-modal therapy, including chemotherapy, **radiation** therapy and surgery. Response rates of localized or disseminated SCLC remain high to systemic chemotherapy, however, persistence of the primary **tumor** and persistence of the **tumor** in the associated lymph nodes has led to the integration of several therapeutic modalities in the treatment of SCLC.

DETD Additionally, **radiation** therapy in conjunction with the preferred combinations of angiogenesis inhibitors and systemic chemotherapy is contemplated to be effective at increasing the response rate for SCLC patients. The typical dosage regimen for **radiation** therapy ranges from 40 to 55 Gy, in 15 to 30 fractions, 3 to 7 times week. The tissue volume. . .

DETD In the treatment of locally advanced non-inflammatory breast cancer, a COX-2 inhibitor and **radiation** therapy can be used to treat the disease in combination with other antiangiogenic agents, or in combination with surgery, or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, and surgery that can be used in combination with the **radiation** therapy and COX-2 inhibitors include, but are not limited to: 1) doxorubicin, vincristine; 2) cyclophosphamide, doxorubicin, 5-flourouracil, vincristine, prednisone; 3). . .

DETD In the treatment of locally advanced inflammatory breast cancer, COX-2 inhibitors and **radiation** therapy can be used to treat the disease in combination with other antiangiogenic agents, or in combination with surgery, or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, **radiation** therapy and surgery that can be used in combination with the COX-2 inhibitors and **radiation** include, but or not limited to: 1) cyclophosphamide, doxorubicin, 5-fluorouracil; 2) cyclophosphamide, doxorubicin, 5-fluorouracil, mastectomy; 3) 5-flurouracil, doxorubicin, clyclophosphamide, vincristine,. . .

DETD In the treatment of metastatic breast cancer, **radiation** therapy and COX-2 inhibitors are used to treat the disease in

combination with surgery, or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, and surgery that can be used in combination with the **radiation** therapy and COX-2 inhibitors include, but are not limited to: 1) cyclosphosphamide, methotrexate, 5-fluorouracil; 2) cyclophosphamide, adriamycin, 5-fluorouracil; 3) cyclosphosphamide,. . .

DETD In the treatment of superficial bladder cancer, COX-2 inhibitors and **radiation** therapy are used to treat the disease in combination with surgery (TUR), and intravesical therapies.

DETD In the treatment of muscle-invasive bladder cancer, **radiation** therapy and COX-2 inhibitors can be used to treat the disease in combination with other antiangiogenic agents, or in combination. . .

DETD The preferred **radiation** dose is between 5,000 to 7,000 cGY in fractions of 180 to 200 cGY to the tumor. Additionally, 3,500 to 4,700 cGY total dose is administered to the normal bladder and pelvic contents in a four-field technique. **Radiation** therapy should be considered only if the patient is not a surgical candidate, but may be considered as preoperative therapy.

DETD The preferred combination of chemotherapeutic agents that can be used in combination with **radiation** therapy and the COX-2 inhibitors is cisplatin, methotrexate, vinblastine.

DETD In the treatment of metastatic bladder cancer, a combination of **radiation** therapy and COX-2 inhibitors can be used to treat the disease in combination with surgery, or with chemotherapeutic agents.

DETD Preferred combinations that can be used along with a combination of **radiation** therapy and a COX-2 inhibitor for the treatment of malignant glioma include: 1) BCNU (carmustine); 2) methyl CCNU (lomustine); 3). . . hydroxyurea, procarbazine, VM-26; 10) BNCU, 5-flourouacil; 11) methyl CCNU, dacarbazine; 12) misonidazole, BCNU; and 13) PCNU. The preferred dose of **radiation** therapy is about 5,500 to about 6,000 cGY. Preferred radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR).

DETD . . . The end points of the treatment were tumor growth delay (days) and TCD.sub.50 (tumor control dose 50, defined as the **radiation** dose yielding local tumor cure in 50% of irradiated mice 120 days after irradiation). To obtain tumor growth curves, three. . .

DETD . . . of 6.31 Gy/minute. During irradiation, unanesthetized mice were immobolized on a jig and the tumor was centered in a circular **radiation** field 3 cm in diameter. Regression and regrowth of tumors were followed at 1-3 day intervals until the tumor diameter. . . 2 plots the growth curves to illustrate the effect of a COX-2 inhibitor on tumor growth when combined with a **radiation** dose of 30 Gy. Day 0 designates the time of tumor irradiation; it should be noted, however, that tumors in. . .

DETD The magnitude of tumor growth delay as a function of **radiation** dose with or without treatment with a COX-2 inhibitor was plotted (FIG. 3) to determine the enhancement of tumor response to **radiation** . This requires that tumor growth delay after **radiation** be expressed only as the absolute tumor growth delay, i.e., the time in days for tumors treated with **radiation** to grow from 8 to 12 mm in diameter minus the time in days for untreated tumors to reach the same size. It also requires that the effect of the combined a COX-2 inhibitor plus-**radiation** treatment be expressed as the normalized tumor growth delay. Normalized tumor growth delay is defined as the time for tumors treated with both a COX-2 inhibitor and **radiation** to grow from 8 to 12 mm in diameter minus the time in days for tumors treated with a COX-2. . . Absolute tumor growth delay and normalized tumor growth delay along with their 95% confidence

intervals were plotted for all three **radiation** doses used in this experiment (30, 40, and 50 Gy). The enhancement factor was 3.64 (95% confidence interval 3.42-3.86), obtained. . . fit the ratio of the slopes of the two lines. While no tumors were cured by any of the three **radiation** doses given alone, tumors in one of six, in two of six, and in one of eight animals were cured when a COX-2 inhibitor treatment was combined with **radiation** treatment at 30, 40, and 50 Gy, respectively. Two of eight mice in the group that received the COX-2 inhibitor. . .

DETD . . . COX-2 inhibitor and local tumor irradiation was the same as that described in FIGS. 2-3. Here, the single doses of .gamma.-**radiation** ranged from 25 to 80 Gy. Mice were checked for the presence of tumor at the irradiated site at 2-. . . for up to 120 days, at which time TCD.sub.50 values were calculated. TCD.sub.50 values (tumor control dose 50 designates a **radiation** dose yielding 50% control [regression] of local tumor) were computed by use of the logistic model (Finney, Quartel response and the tolerance distribution. Statistical methods in biological Assay, 2.sup.nd Ed., 1952) and shown in FIG. 4 (.cndot.-**radiation** only and .tangle-solidup.-COX-2 inhibitor plus **radiation**. Horizontal bars represent 95% confidence intervals, at the TCD.sub.50 dose level. Five of 60 mice that received a COX-2 inhibitor plus **radiation** died of unknown causes. The dead mice were excluded from TCD .sub.5 analysis. TCD.sub.50 assays contained 57 mice that received **radiation** only and 55 mice that received a combination of the COX-2 inhibitor and **radiation**.

DETD . . . 13.6 days (95% CI=10.5-16.7 days), and mice treated with both agents required 43.5 days (95% CI=30.8-56.2 days) (P=0.001 compared with **radiation**-only group). The efficacy of irradiation was enhanced by a factor of 3.64 (95% CI=3.42-3.86), determined from the curves in FIG. 3, which plot the magnitude of tumor growth delay as a function of **radiation** dose with or without treatment with a COX-2 inhibitor. This compound also greatly enhanced the tumor cure rate after irradiation. . . in the combination-treatment group. The enhancement factor was 1.77 (95% CI=1.5 1-1.99). obtained by dividing the TCD.sub.50 value of the **radiation**-alone group by the combination-treatment group. The 95% CI's were obtained by use of Fieller's theorem (Heron, J. Statist. Comput. Simul.,. . .

DETD A COX-2 inhibitor dramatically enhanced the tumor response to **radiation**, as evidenced by the increase in tumor growth delay and the augmentation of tumor curability. The enhancement factors were 3.64 and 1.77, respectively, greater than the enhancement factors of 1.4 and 1.26 for **radiation**-indomethacin and **radiation** alone, respectively.

CLM What is claimed is:

. . . neoplasia in a subject in need of such treatment wherein the method comprises treating the subject with an amount of **radiation** and a **radiation**-potentiating amount of a COX-2 inhibiting compound selected from the group consisting of celecoxib and 4-[5-(4-chlorophenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide wherein: the amount of **radiation** and the amount of the COX-2 inhibiting compound together comprise a neoplasia-treating-effective amount of the COX-2 inhibiting compound and the **radiation**; and the neoplasia is sensitive to such treatment.

2. The method of claim 1 wherein the **neoplasia** is selected from the group consisting of **lung cancer**; breast **cancer**; gastrointestinal **cancer**; bladder **cancer**; head and neck **cancer**; cervical **cancer**

; colorectal **cancer**; prostate **cancer**; and pancreatic **cancer**.

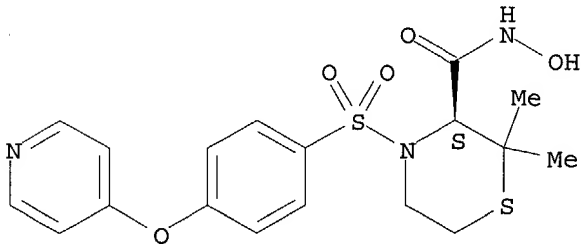
3. The method of claim 2 wherein the **neoplasia** is **lung cancer**.

17. A method for treating a neoplasia in a subject in need of such treatment wherein the method comprises treating the subject with an amount of **radiation** and a **radiation**-potentiating amount of a COX-2 inhibiting compound selected from the group consisting of celecoxib and 4-[5-(4-chlorophenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide wherein: the amount of **radiation** and the amount of the COX-2 inhibiting compound together comprise a neoplasia-treating-effective amount of the COX-2 inhibiting compound and the **radiation**; the amount of the COX-2 inhibiting compound is at least about 6 mg/kg of body weight per day; and the. . . . . neoplasia in a subject in need of such treatment wherein the method comprises treating the subject with an amount of **radiation** and a **radiation**-potentiating amount of a COX-2 inhibiting compound selected from the group consisting of celecoxib and 4-[5-(4-chlorophenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide wherein: the amount of **radiation** and the amount of the COX-2 inhibiting compound together comprise a neoplasia-treating-effective amount of the COX-2 inhibiting compound and the **radiation**; the amount of the COX-2 inhibiting compound is in the range of about 0.1 mg to about 10,000 mg per. . .

IT 50-18-0, Cyclophosphamide 51-21-8, Fluorouracil 52-24-4, Thiotepa 53-86-1, Indomethacin 57-22-7, Vincristine 58-05-9, Leucovorin 76-43-7, Fluoxymesterone 128-13-2, Ursodeoxycholic acid 302-79-4, Retinoic acid 471-34-1, Calcium carbonate, biological studies 865-21-4, Vinblastine 1464-42-2, Selenomethionine 3562-63-8, Megestrol 7782-49-2, Selenium, biological studies 10540-29-1, Tamoxifen 14769-73-4, Levamisole 15663-27-1, Cisplatin 15866-90-7 23214-92-8, Doxorubicin 33069-62-4, Paclitaxel 33419-42-0, Etoposide 41575-94-4, Carboplatin 51803-78-2 59973-80-7, Sulindac sulfone 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 65807-02-5, Goserelin 70052-12-9, Eflornithine 71486-22-1, Vinorelbine 80937-31-1 84449-90-1, Raloxifene 89778-26-7, Toremifene 93014-16-5 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 107868-30-4, Exemestane 112809-51-5, Letrozole 114977-28-5, Docetaxel 120511-73-1, Anastrozole 123653-11-2 123663-49-0 123948-87-8, Topotecan 154039-60-8 154361-50-9, Capecitabine 158205-05-1 158959-32-1 162011-90-7, Rofecoxib 162054-19-5 169590-42-5, Celecoxib 170569-86-5 170569-87-6 170569-88-7 170630-40-7 177660-77-4 177660-95-6 178816-61-0 178816-94-9, [1,1':2',1''-Terphenyl]-4-sulfonamide 179382-91-3 179545-77-8 180200-68-4, JTE-522 181485-41-6 181695-72-7, Valdecoxib 181695-81-8 181696-33-3 187845-71-2 187845-80-3 189954-13-0 189954-16-3 191537-76-5 **192329-42-3** 197239-97-7 197239-99-9 197240-09-8 197240-14-5 197904-84-0 197905-01-4 198470-84-7 212126-32-4 215123-80-1 226388-60-9 226388-66-5 226389-91-9 226395-57-9 226395-66-0 226395-67-1 226395-93-3 226396-02-7 226396-03-8 226396-26-5 226703-01-1 227619-96-7 251972-30-2, SC-58236 279221-12-4 279221-13-5 279221-14-6 279221-15-7 279221-16-8 279221-17-9 279221-18-0 279221-19-1 279221-20-4 279221-21-5 279221-22-6 279221-23-7 279221-24-8 279221-25-9 279221-26-0 279221-27-1 279221-28-2
(cyclooxygenase-2 inhibitor and matrix metalloproteinase inhibitor in combination therapy for neoplasia treatment)

IT **192329-42-3**
(cyclooxygenase-2 inhibitor and matrix metalloproteinase inhibitor in combination therapy for neoplasia treatment)
RN 192329-42-3 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 3 OF 5 USPATFULL on STN
AB There are disclosed compounds of the formula ##STR1##

a prodrug thereof, or a pharmaceutically acceptable salt, solvate or isomer of said compound or of said prodrug, which are useful for the treatment of chemokine-mediated diseases such as acute and chronic inflammatory disorders and cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:141162 USPATFULL
TITLE:	3,4-Di-substituted cyclobutene-1,2-diones as CXC chemokine receptor antagonists
INVENTOR(S):	Taveras, Arthur G., Denville, NJ, UNITED STATES Aki, Cynthia J., Livingston, NJ, UNITED STATES Bond, Richard W., Union, NJ, UNITED STATES Chao, Jianping, Summit, NJ, UNITED STATES Dwyer, Michael, Scotch Plains, NJ, UNITED STATES Ferreira, Johan A., Bensalem, PA, UNITED STATES Pachter, Jonathan A., Maplewood, NJ, UNITED STATES Baldwin, John J., Gwynedd Valley, PA, UNITED STATES Kaiser, Bernd, Plainsboro, NJ, UNITED STATES Li, Ge, ShangHai, CHINA Merritt, J. Robert, Ewing, NJ, UNITED STATES Nelson, Kingsley H., JR., Mebane, NC, UNITED STATES Rokosz, Laura L., Union, NJ, UNITED STATES
PATENT ASSIGNEE(S):	Schering Corporation (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003097004	A1	20030522	
APPLICATION INFO.:	US 2002-62006	A1	20020201	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-265951P	20010202	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1,

1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
LINE COUNT: 2505
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . antineoplastic agent or anti-angiogenesis agent or VEGF receptor kinase inhibitor or antibodies against the VEGF receptor or interferon, and/or c) **radiation**.

SUMM . . . antineoplastic agent, a microtubule affecting agent or an anti-angiogenesis agent. Additionally, the compounds of the invention can be co-administered with **radiation** therapy.

SUMM [0126] The amount and frequency of administration of the compounds of formula (I) and the chemotherapeutic agents and/or **radiation** therapy will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and. . .

SUMM [0127] The chemotherapeutic agent and/or **radiation** therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or **radiation** therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or **radiation** therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts. . . of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., antineoplastic agent or **radiation**) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

SUMM . . . the methods of this invention, a compound of formula (I) is administered concurrently or sequentially with a chemotherapeutic agent and/or **radiation**. Thus, it is not necessary that, for example, the chemotherapeutic agent and the compound of formula (I), or the **radiation** and the compound of formula (I), should be administered simultaneously or essentially simultaneously. The advantage of a simultaneous or essentially. . .

SUMM [0130] The particular choice of a compound of formula (I), and chemo-therapeutic agent and/or **radiation** will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the. . .

SUMM [0131] The compound of formula (I), and chemotherapeutic agent and/or **radiation** may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or **radiation** to be administered in conjunction (i.e., within a single treatment protocol) with the compound of formula (I).

SUMM [0132] If the compound of formula (I), and the chemotherapeutic agent and/or **radiation** are not administered simultaneously or essentially simultaneously, then the initial order of administration of the compound of formula (I), and the chemotherapeutic agent and/or **radiation**, may not be important. Thus, the compound of formula (I) may be administered first followed by the administration of the chemotherapeutic agent and/or **radiation**; or the chemotherapeutic agent and/or **radiation** may be administered first followed by the administration of the compound of formula (I). This alternate administration may be repeated. . . physician after evaluation of the disease being treated and the condition of the

patient. For example, the chemotherapeutic agent and/or **radiation** may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the compound of formula (I) followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or **radiation**, and so on until the treatment protocol is complete.

SUMM . . . can modify each protocol for the administration of a component (therapeutic agent--i.e., the compound of formula (I), chemotherapeutic agent or **radiation**) of the treatment according to the individual patient's needs, as the treatment proceeds.

CLM What is claimed is:

27. The method of claim 26 which further comprises administering to the patient at least one anti-cancer agent and/or **radiation** therapy.

35. The method of claim 26 wherein the **cancerous tumor** type is melanoma, gastric carcinoma or non-small cell **lung** carcinoma.

36. The method of claim 35 which further comprises administering to the patient at least one anti-cancer agent and/or **radiation** therapy.

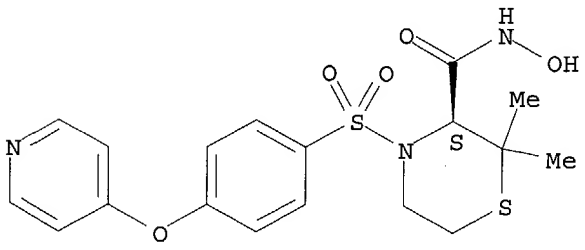
IT 50-35-1, Thalidomide 145-63-1, Suramin 15866-90-7, Col-3 33069-62-4, Taxol 37270-94-3, Platelet factor 4 38101-59-6, Im862 86090-08-6, Angiostatin 99519-84-3, CAI 114977-28-5, Taxotere 129298-91-5, Tnp-470 148717-90-2, Squalamine 154039-60-8, Marimastat 169799-04-6, Cgs27023a 187888-07-9, Endostatin 188968-51-6, Emd121974 **192329-42-3**, Ag3340 204005-46-9, Su-5416 212142-18-2, PTK 787 216974-75-3 252916-29-3, Su-6668 259188-38-0, Bms-275291 305838-77-1, Neovastat 324740-00-3, Vitaxin 386211-13-8, Zd-101 443913-73-3, Zd-6474
(coadministration; prepn. of 3,4-diaminobutene-1,2-diones as CXC chemokine receptor antagonists)

IT **192329-42-3**, Ag3340
(coadministration; prepn. of 3,4-diaminobutene-1,2-diones as CXC chemokine receptor antagonists)

RN 192329-42-3 USPATFULL

CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 4 OF 5 USPATFULL on STN

AB The present invention provides methods and compositions for the treatment and prevention of any of a large number of diseases and conditions with an angiogenic component, e.g., cancer. The present

invention is based upon the discovery that liposome-encapsulated chemotherapeutic agents, such as alkaloids (e.g., vinca alkaloids such as vincristine), are surprisingly effective at treating such diseases or conditions when administered at a higher frequency than those used with conventional administration strategies. Such methods can be used to treat diseases such as cancer even when the cancer comprises cells that are resistant to the chemotherapeutic alkaloid. The liposome encapsulation of the chemotherapeutic agents, e.g., alkaloids, imparts dramatic improvements in the stability, biodistribution, and delivery of the agents, thereby allowing more efficacious and convenient administration to a patient with any of the herein-described diseases or conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:119743 USPATFULL
TITLE:	Anti-angiogenic therapy using liposome-encapsulated chemotherapeutic agents
INVENTOR(S):	Flowers, Clay, Surrey, CANADA Saltman, David, Vancouver, CANADA Tam, Patrick M.S., Vancouver, CANADA Burge, Clive T.R., Brentwood Bay, CANADA Hasrasym, Troy O., Vancouver, CANADA
PATENT ASSIGNEE(S):	Inex Pharmaceuticals Corporation, Burnaby, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003082228	A1	20030501	
APPLICATION INFO.:	US 2002-143545	A1	20020509	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-289935P	20010509 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS:	33
EXEMPLARY CLAIM:	1
LINE COUNT:	1734

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0011] In one embodiment, the disease or condition is **cancer** (e.g., prostate, **lung**, breast, colon, kidney, stomach, bladder, or ovarian **cancer**, multiple myeloma, etc.). In another embodiment, the chemotherapeutic agent is a vinca alkaloid. In another embodiment, the vinca alkaloid is. . .

SUMM . . . about 50% in response to a treatment. The treatment can be any treatment directed against cancer, but typically includes chemotherapy, **radiation** therapy, hormone therapy, surgery, cell or bone marrow transplantation, immunotherapy, and others. The size of a tumor can be detected. . .

SUMM . . . state, as measured by, for example, tumor size and/or cancer marker levels, has disappeared following a treatment such as chemotherapy, **radiation** therapy, hormone therapy, surgery, cell or bone marrow transplantation, or immunotherapy. The presence of a tumor can be detected by. . .

SUMM [0034] "**Radiation** therapy" refers to the administration of radioactivity to an animal with cancer. **Radiation** kills or inhibits the growth of dividing cells, such as cancer cells.

SUMM . . . to treat or prevent any disease or condition associated with angiogenesis. In a preferred embodiment, the disease or condition is **cancer**. Any type of **cancer** can be treated using these methods including, but not limited to, **lung cancer**, breast **cancer**, gastrointestinal **cancers**, prostate **cancer**, liver **cancer**, colorectal **cancer**, lymphomas, leukemias, skin **cancer**, myelomas, kidney **cancer**, neuroblastomas, small cell **lung cancer** , bladder **cancer**, bone **cancer**, CNS **cancers** , ovarian **cancer**, pancreatic **cancer**, sarcomas, testicular **cancer**, or any other type of **cancer**.

SUMM . . . number of different experimental animal models. For example, to evaluate the ability of a particular regimen to treat or prevent **cancer**, any of a large number of animal models for **cancer** can be used. Often, **cancerous** cells (e.g., cell lines derived from a **tumor**) or any cells that are capable of forming a **tumor** in vivo, are introduced into an animal, e.g., a mouse. The effect of a compound on **tumorigenesis** is then assessed by, e.g., allowing **tumors** to grow and then administering the compound to determine whether the growth of the **tumors** is slowed, arrested, or reversed. By introducing cells of varying types (e.g., breast **cancer** cells, **lung cancer** cells, lymphoma cells, etc.), and by varying the method and site of introduction of the cells (e.g., intravenous, subcutaneous, etc.) the effect of the compound on various **tumor** types can be assessed. See, e.g., Examples I and II, infra.

SUMM [0088] In one embodiment, the effect of a particular administration protocol on angiogenesis can, e.g., be directly assessed by introducing **tumorigenic** cells that are resistant to a particular compound, e.g., either naturally or by selection in vitro or in vivo. When. . . introduced into an animal, and the compound is administered using the present methods, any effect on the growth of the **tumor** necessarily occurs by an inhibition of angiogenesis, rather than by an effect on the **tumor** cells themselves. Examples of cells that can be used in such methods include, but are not limited to, Lewis **Lung** carcinoma cells and NCI-H69 small cell **lung cancer** cells, which can, e.g., be selected in vitro or in vivo for resistance to the alkaloid.

SUMM . . . (IDEC Pharmaceuticals Corporation). In addition, liposome-encapsulated vinca alkaloids can be administered along with one or more non-molecular treatments such as **radiation** therapy, bone marrow transplantation, hormone therapy, surgery, etc.

DETD Evaluation of the Efficacy of Varying Drug-to-Lipid Ratios of VSLI in the LX-1, CT-26 and Lewis **Lung Tumor** Models

DETD . . . Injections were administered intravenously in the tail vein in approximately 200 .mu.l as indicated in the table below. For solid **tumor** models, Lewis **Lung** and LX-1, treatments were initiated when **tumors** reach a size of 20 to 70 mm.sup.3. For the CT-26 intrasplenic study, mice were treated 24-hours after **tumor** cell implantation.

Group	Drug Treatment (D/L)	Schedule	Dose	Total Dose	Mice/group
LX-1					
A	Vincristine	Q3dx7	0.21 mg/kg	1.5 mg/kg	5

B	VSLI. . .	mg/kg	2.0 mg/kg	5	
C	VSLI (0.05)	Q3dx7	0.29 mg/kg	2.0 mg/kg	5
D	VSLI (0.01)	Q3dx7	0.29 mg/kg	2.0 mg/kg	5

Lewis **Lung**

A	Vincristine	Q3dx7	0.21 mg/kg	1.5 mg/kg	5
B	VSLI (0.1)	Q3dx7	0.29 mg/kg	2.0 mg/kg	5
C	VSLI (0.05)	Q3dx7	0.29 mg/kg. . .		

DETD Evaluation of the Efficacy of VSLI in Treating Drug Resistant Lewis **Lung Tumor** in a Multiple Low Dose Treatment Schedule

DETD . . . old female C57BL6/J mice at 23-28 grams are used in this procedure. These mice are commonly used for propagating Lewis **Lung** Carcinoma and the strain is recommended by American Type Culture Collection. In the first phase, the MTD will be determined. . . LLC/VCR cells will be injected and subjected to VCR or VSLI at the MTD Dose. Cells obtained from the resistant **tumors** will be exposed to vincristine in vitro to confirm the resistance phenotype. Those cells found to have the resistance phenotype. . .

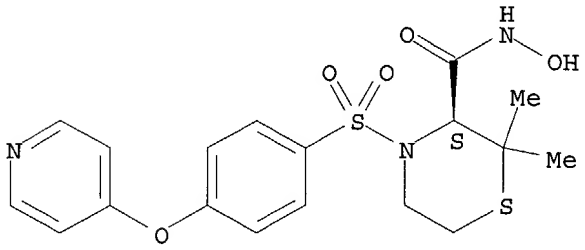
IT 50-35-1, Thalidomide 57-22-7, Vincristine 865-21-4, Vinblastine 7689-03-4, Camptothecin 7689-03-4D, Camptothecin, analogs 9000-94-6D, Antithrombin III, fragment 9002-62-4D, Prolactin, deriv. 15866-90-7, COL-3 37270-94-3D, Platelet factor 4, fragment 38101-59-6, IM862 71486-22-1, Vinorelbine 82855-09-2, Combretastatin 86090-08-6, Angiostatin 98724-27-7, Proliferin-related protein 99519-84-3, CAI 123948-87-8, Topotecan 129298-91-5, TNP-470 148717-90-2, Squalamine 154039-60-8, Marimastat 169799-04-6, CGS-27023A 187888-07-9, Endostatin 188968-51-6, EMD121974 **192329-42-3**, AG3340 194368-66-6, Angiopoietin 2 204005-46-9, SU5416 212142-18-2, PTK787 305838-77-1, Neovastat 324740-00-3, Vitaxin 474940-55-1, PIK 787/2K22584
(anti-angiogenic therapy using liposome-encapsulated chemotherapeutic agents for treatment of diseases such as cancer)

IT **192329-42-3**, AG3340
(anti-angiogenic therapy using liposome-encapsulated chemotherapeutic agents for treatment of diseases such as cancer)

RN 192329-42-3 USPATFULL

CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 5 OF 5 USPATFULL on STN

AB The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:37157 USPATFULL
TITLE: Methods for enhancing antibody-induced cell lysis and treating cancer
INVENTOR(S): Weiner, George, Iowa City, IA, UNITED STATES
Hartmann, Gunther, Munich, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003026801	A1	20030206
APPLICATION INFO.:	US 2001-888326	A1	20010622 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-213346P	20000622 ~~(60)~~

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Alan W. Steele, Wolf, Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 77
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 4637
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] **Cancer** is the second leading cause of death, resulting in one out of every four deaths in the United States. In 1997, the estimated total number of new diagnoses for **lung**, breast, prostate, colorectal and ovarian **cancer** was approximately two million. Due to the ever increasing aging population in the United States, it is reasonable to expect that rates of **cancer** incidence will continue to grow.

SUMM . . . BRCA gene mutation for breast cancer, APC for colon cancer), exposure to suspected cancer-causing agents, or carcinogens (e.g., asbestos, UV **radiation**) and familial disposition for particular cancers such as breast cancer.

SUMM [0005] Cancer is currently treated using a variety of modalities including surgery, **radiation** therapy and chemotherapy. The choice of treatment modality will depend upon the type, location and dissemination of the cancer. For example, surgery and **radiation** therapy may be more appropriate in the case of solid well-defined tumor masses and less practical in the case of non-solid tumor cancers such as leukemia and lymphoma. One of the advantages of surgery and **radiation** therapy is the ability to control to some extent the impact of the therapy, and thus to limit the toxicity to normal tissues in the body. However, surgery and **radiation** therapy are often followed by chemotherapy to guard against any remaining or radio-resistant cancer cells. Chemotherapy is also the most. . .

SUMM [0021] The **cancer** may be selected from the group consisting of basal cell carcinoma, bladder **cancer**, bone **cancer**, brain and central nervous system (CNS) **cancer**, breast **cancer**, cervical **cancer**, colon and rectum **cancer**, connective tissue **cancer**, esophageal **cancer**, eye **cancer**, kidney **cancer**, larynx **cancer**, leukemia, liver **cancer**, **lung** **cancer**, Hodgkin's lymphoma, non-Hodgkin's lymphoma, melanoma, myeloma, oral cavity **cancer** (e.g., lip, tongue, mouth, and pharynx), ovarian **cancer**, pancreatic **cancer**, prostate **cancer**, rhabdomyosarcoma, skin **cancer**, stomach **cancer**, testicular **cancer**, and uterine **cancer**. In preferred embodiments, the **cancer** to be

treated may be selected from the group consisting of bone **cancer**, brain and CNS **cancer**, connective tissue **cancer**, esophageal **cancer**, eye **cancer**, Hodgkin's lymphoma, larynx **cancer**, oral cavity **cancer** (e.g., lip, tongue, mouth, and pharynx), skin **cancer**, and testicular **cancer**.

DETD [0057] **Cancers** include, but are not limited to, basal cell carcinoma, biliary tract **cancer**; bladder **cancer**; bone **cancer**; brain and CNS **cancer**; breast **cancer**; cervical **cancer**; choriocarcinoma; colon and rectum **cancer**; connective tissue **cancer**; **cancer** of the digestive system; endometrial **cancer**; esophageal **cancer**; eye **cancer**; **cancer** of the head and neck; gastric **cancer**; intra-epithelial **neoplasm**; kidney **cancer**; larynx **cancer**; leukemia; liver **cancer**; **lung cancer** (e.g., small cell and non-small cell); lymphoma including Hodgkin's and non-Hodgkin's lymphoma; melanoma; myeloma; neuroblastoma; oral cavity **cancer** (e.g., lip, tongue, mouth, and pharynx); ovarian **cancer**; pancreatic **cancer**; prostate **cancer**; retinoblastoma; rhabdomyosarcoma; rectal **cancer**; renal **cancer**; **cancer** of the respiratory system; sarcoma; skin **cancer**; stomach **cancer**; testicular **cancer**; thyroid **cancer**; uterine **cancer**; **cancer** of the urinary system, as well as other carcinomas and sarcomas.

DETD . . . 10 years of age are likely to succumb to the disease. The most common treatment options include surgery, chemotherapy and **radiation** therapy. Other treatment modalities which have been used with some success are laser therapy, cryotherapy, hyperthermia and immunotherapy. The choice. . .

DETD [0059] Malignant disorders commonly diagnosed in dogs and cats include but are not limited to lymphosarcoma, osteosarcoma, mammary **tumors**, mastocytoma, brain **tumor**, melanoma, adenosquamous carcinoma, carcinoid **lung tumor**, bronchial gland **tumor**, bronchiolar adenocarcinoma, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, retinoblastoma, Ewing's sarcoma, Wilms' **tumor**, Burkitt's lymphoma, microglioma, neuroblastoma, osteoclastoma, oral **neoplasia**, fibrosarcoma, osteosarcoma and rhabdomyosarcoma. Other **neoplasias** in dogs include genital squamous cell carcinoma, transmissable venereal **tumor**, testicular **tumor**, seminoma, Sertoli cell **tumor**, hemangiopericytoma, histiocytoma, chloroma (granulocytic sarcoma), corneal papilloma, corneal squamous cell carcinoma, hemangiosarcoma, pleural mesothelioma, basal cell **tumor**, thymoma, stomach **tumor**, adrenal gland carcinoma, oral papillomatosis, hemangioendothelioma and cystadenoma. Additional malignancies diagnosed in cats include follicular lymphoma, intestinal lymphosarcoma, fibrosarcoma and. . . cell carcinoma. The ferret, an ever-more popular house pet, is known to develop insulinoma, lymphoma, sarcoma, neuroma, pancreatic islet cell **tumor**, gastric MALT lymphoma and gastric adenocarcinoma.

DETD [0060] **Neoplasias** affecting agricultural livestock include leukemia, hemangiopericytoma and bovine ocular **neoplasia** (in cattle); preputial fibrosarcoma, ulcerative squamous cell carcinoma, preputial carcinoma, connective tissue **neoplasia** and mastocytoma (in horses); hepatocellular carcinoma (in swine); lymphoma and pulmonary adenomatosis (in sheep); pulmonary sarcoma, lymphoma, Rous

sarcoma, reticuloendotheliosis, fibrosarcoma, nephroblastoma, B-cell lymphoma and lymphoid leukosis (in avian species); retinoblastoma, hepatic **neoplasia**, lymphosarcoma (lymphoblastic lymphoma), plasmacytoid leukemia and swimbladder sarcoma (in fish), caseous lymphadenitis (CLA): chronic, infectious, contagious disease of sheep and goats caused by the bacterium Corynebacterium pseudotuberculosis, and contagious **lung tumor** of sheep caused by jaagsiekte.

DETD . . . treatment methods, the invention is aimed at administering the compositions of the invention to a subject at risk of developing **cancer**. A subject at risk of developing a **cancer** is one who has a high probability of developing **cancer**. These subjects include, for instance, subjects having a genetic abnormality, the presence of which has been demonstrated to have a correlative relation to a higher likelihood of developing a **cancer**. Subjects exposed to **cancer**-causing agents such as tobacco, asbestos, or other chemical toxins are also subjects at risk of developing **cancers** used herein. When a subject at risk of developing a **cancer** is treated with an immunostimulatory nucleic acid, an antibody and optionally a **cancer** therapy, on a regular basis, such as monthly, the **cancer** growth will be prevented from initiating. This aspect of the invention is particularly advantageous when the subjects employed in certain trades which are exposed to **cancer**-causing agents on an ongoing basis. For example, many airborne, or inhaled, carcinogens such as tobacco smoke and asbestos have been associated with **lung cancer**.

DETD . . . of neoplasms in subjects, usually by affecting DNA directly. Carcinogens may take one of several forms such as chemical, electromagnetic **radiation**, or may be an inert solid body.

DETD . . . to radon, Iron and steel founding, Isopropyl alcohol manufacture (strong acid process), Manufacture of magenta, Melphalan, 8-Methoxypsoralen (Methoxsalen) plus ultraviolet **radiation**, Mineral oils-untreated and mildly-treated oils, MOPP and other combined chemotherapy for cancer, Mustard gas (sulphur mustard), 2-Naphthylamine, Nickel and nickel. . . all in group), Painter (occupational exposure as a painter), Phenacetin (analgesic mixtures containing), Rubber industry, Salted fish (Chinese style), Solar **radiation**, Shale oils, Soots, Sulphuric acid (occupational exposures to strong-inorganic-acid mists of sulphuric acid), Talc containing asbestiform fibres, Thiotepa, Tobacco products. . .

DETD . . . N-Nitrosodimethylamine, Petroleum refining (occupational refining exposures), Phenacetin, Polychlorinated biphenyls, Procarbazine hydrochloride, Silica (crystalline), Styrene-7,8-oxide, Tris(1-azaridinyl)phosphine sulphide (Thiotepa), Tris(2,3-dibromopropyl) phosphate, Ultraviolet **radiation**: A, B and C including sunlamps and sunbeds, and Vinyl bromide.

DETD [0068] Subjects at risk of developing **cancer** also include those who have a genetic predisposition to **cancer**. In many cases, genetic predisposition to **cancer** can be identified by studying the occurrence of **cancer** in family members. Examples of genetic predisposition to common forms of **cancer** include, but are not limited to, mutation of BRCA1 and BRCA2 in familial breast **cancer**, mutation of APC in familial colony **cancer** (familial polyposis coli), mutation of MSH2 and MLH1 in hereditary nonpolyposis colon **cancer** (HNPCC), mutation of p53 in Li-Fraumeni syndrome, mutation of Rb1 in retinoblastoma, mutation of RET in multiple endocrine **neoplasia** type 2 (MEN2), mutation of VHL in renal **cancer** and mutation of WT1 in Wilms' **tumor**. Other **cancers** for which a familial predisposition has been

identified include ovarian, prostate, melanoma and **lung cancer**.

DETD [0069] It has been estimated that almost half of all currently diagnosed **cancers** will be treated with some form of **cancer** medicament. However, many forms of **cancer**, including melanoma, colorectal, prostate, endometrial, cervical and bladder **cancer**, do not respond well to treatment with **cancer** medicaments. In fact, only about 5-10 percent of **cancers** can be cured using **cancer** medicaments alone. These include some forms of leukemias and lymphomas, testicular **cancer**, choriocarcinoma, Wilms' **tumor**, Ewing's sarcoma, neuroblastoma, small-cell **lung cancer** and ovarian **cancer**. Treatment of still other **cancers**, including breast **cancer**, requires a combination therapy of surgery or radiotherapy in conjunction with a **cancer** medicament.

DETD . . . isotype antibodies are well known in the art and include at least the antibodies listed in Table 2 below.

TABLE 2

Cancer Immunotherapies In Development Or On The Market.

Marketer	Brand Name (Generic Name)
Indication	
IDEC/Genentech, (IDEC-Inc./Hoffmann-LaRoche (first monoclonal antibody licensed for the treatment of **cancer** in the U.S.)	Rituxan .TM. (rituximab, Mabthera) C2B8, chimene murine/human anti-CD20 MAb)
non-Hodgkin's lymphoma	
Genentech/Hoffmann-La Roche	Herceptin, anti-Her2 hMAb
Breast/ovarian	
Cytogen Corp.	Quadramet (CYT-424) radiotherapeutic agent
Bone metastases	
Centocor/Glaxo/Ajinomoto	Panorex .RTM. (17-1A) (murine monoclonal antibody)
Adjuvant therapy for colorectal (Dukes-C)	
Centocor/Ajinomoto	Panorex .RTM. (17-1A) (chimeric murine monoclonal antibody)
Pancreatic, **lung**, breast, ovary	
IDEC	IDEC-Y2B8 (murine, anti-CD20 MAb labeled with Yttrium-90)
non-Hodgkin's lymphoma	
ImClone Systems	BEC2 (anti-idiotypic MAb, mimics the epitope) (with BCG)
GD.sub.3 Small cell **lung**	
ImClone Systems	C225 (chimeric monoclonal antibody to epidermal growth factor receptor (EGFr))
Renal cell	
Techniclone International/Alpha Pharmaceuticals, Inc.	Oncolym (Lym-1 monoclonal. . . ATRAGEN .RTM.
Acute promyelocytic leukemia	
ImClone Systems	C225 (chimeric anti-EGFr monoclonal antibody) + cisplatin or
Head & neck, non-small	

radiation cell **lung cancer**

Altarex, Canada Ovarex (B43.13, anti-idiotypic CA125,
Ovarian
mouse MAb)

Coulter Pharma (Clinical results Bexxar (anti-CD20 Mab labeled with
.sup.131I) non-Hodgkin's lymphoma
have been. . . huMAb to the leukocyte antigen Chronic lymphocytic
CAMPATH
leukemia (CLL)

Center of Molecular Immunology ior t6 (anti CD6, murine MAb) CTCL
Cancer

Medarex/Novartis MDX-210 (humanized anti-HER-2 bispecific
Breast, ovarian
antibody)

Medarex/Novartis MDX-210 (humanized anti-HER-2 bispecific
Prostate, non-small cell
antibody)
lung, pancreatic, breast

Medarex MDX-11 (complement activating receptor
Acute myelogenous
(CAR) monoclonal antibody)
leukemia (AML)

Medarex/Novartis MDX-210 (humanized anti-HER-2 bispecific
Renal and colon
. . . labelled antibody) Prostate

Aronex Pharmaceuticals, Inc. ATRAGEN .RTM.
non-Hodgkin's lymphoma

Glaxo Welicome plc 3622W94 MAb that binds to EGP40 (17-1A)
non-small cell **lung**,
pancarcinoma antigen on adenocarcinomas
prostate (adjuvant)

Genentech Anti-VEGF, RhuMAb (inhibits
Lung, breast, prostate,
angiogenesis)
colorectal

Protein Design Labs Zenapax (SMART Anti-Tac (IL-2 receptor)
Leukemia, lymphoma
Ab, humanized)

Protein Design Labs SMART M195 Ab,. . . (chimeric
anti-EGFr monoclonal prostate
antibody) + adriamycin

ImClone Systems BEC2 (anti-idiotypic MAb, mimics the
GD.sub.3 Melanoma
epitope)

Medarex MDX-210 (humanized anti-HER-2 bispecific
Cancer
antibody)

Medarex MDX-220 (bispecific for **tumors**
that express **Lung**, colon, prostate,
TAG-72)
ovarian, endometrial,
pancreatic and gastric

Medarex/Novartis MDX-210 (humanized anti-HER-2 bispecific
Prostate
antibody)

Medarex/Merck KgaA MDX-447 (humanized anti-EGF receptor
EGF receptor **cancers**
bispecific antibody)
(head & neck, prostate,

lung, bladder, cervical, ovarian)	
Medarex/Novartis	MDX-210 (humanized anti-HER-2 bispecific
Comb. Therapy with G-CSF for various **cancers**, esp. breast	antibody)
IDEC	MELIMMUNE-2 (murine monoclonal
Melanoma	antibody therapeutic vaccine)
IDEC	MELIMMUNE-1 (murine monoclonal
Melanoma	antibody therapeutic vaccine)
Immunomedics, Inc.	CEACIDE .RTM. (I-131)
Colorectal and other	
NeoRx	Pretarget .RTM. radioactive antibodies
non-Hodgkin's B cell lymphoma	
Novopharm Biotech, Inc.	NovoMAb-G2 (pancarcinoma specific Ab)
Cancer	
Techniclone Corporation/	TNT (chimeric MAb to histone antigens)
Brain	
Cambridge Antibody Technology	
Techniclone	TNT (chimeric MAb to histone antigens)
Brain	
International/Cambridge Antibody Technology	
Novopharm	Gliomab-H (Monoclonals - Humanized Abs)
Brain, melanomas, neuroblastomas	
Genetics Institute/AHP	GNI-250 Mab
Colorectal	
Merck KgaA	EMD-72000 (chimeric-EGF antagonist)
Cancer	
Immunomedics	LymphoCide (humanized LL2 antibody)
non-Hodgkin's B-cell lymphoma	
Immunex/AHP	CMA 676 (monoclonal antibody conjugate)
Acute myelogenous leukemia	
Novopharm Biotech, Inc.	Monopharm-C
Colon, **lung**, pancreatic	
Novopharm Biotech, Inc.	4B5 anti-idiotype Ab
Melanoma, small-cell **lung**	
Center of Molecular Immunology	ior egf/r3 (anti EGF-R humanzied Ab)
Radioimmunotherapy	
Center of Molecular Immunology	ior c5 (murine MAb colorectal) for radioimmunotherapy
Colorectal	
Creative BioMolecules/	BABS (biosynthetic antibody binding
site) Breast **cancer**	Proteins
Chiron	
ImClone Systems/Chugai	FLK-2 (monoclonal antibody to fetal
liver **Tumor**-associated angiogenesis	kinase-2 (FLK-2))
ImmunoGen, Inc.	Humanized MAb/small-drug conjugate
Small-cell **lung**	

Medarex, Inc.	MDX-260 bispecific, targets GD-2
Melanoma, glioma, neuroblastoma	
Procyon Biophanna, Inc.	ANA Ab
Cancer	
Protein Design Labs	SMART 1D10 Ab
B-cell lymphoma	
Protein Design Labs/Novartis	SMART ABL 364 Ab
Breast, **lung**, colon	
Immunomedics, Inc.	ImmuRAIT-CEA
Colorectal	

DETD . . . used herein, chemotherapeutic agents encompass both chemical and biological agents. These agents function to inhibit a cellular activity which the **cancer** cell is dependent upon for continued survival. Categories of chemotherapeutic agents include alkylating/alkaloid agents, antimetabolites, hormones or hormone analogs, and miscellaneous antineoplastic drugs. Most if not all of these agents are directly toxic to **cancer** cells and do not require immune stimulation. Chemotherapeutic agents which are currently in development or in use in a clinical setting are shown in Table 3 below.

TABLE 3

Cancer Drugs In Development Or On The Market.

Marketer	Brand Name	Generic Name
Indication		
Abbott	TNP 470/AGM 1470	Fragyline
Anti-Angiogenesis in **Cancer**		
Takeda	TNP 470/AGM 1470	Fragyline
Anti-Angiogenesis in **Cancer**		
Scotia	Meglamine GLA	Meglamine GLA
Bladder **Cancer**		
Medeva	Valstar	Valrubicin
Bladder **Cancer** - Refractory in situ carcinoma		
Medeva	Valstar	Valrubicin
Bladder **Cancer** - Papillary **Cancer**		
Rhone Poulenc	Gliadel Wafer	Carmustaine + Polifepr Osan
Brain **Tumor**		
Warner Lambert	Undisclosed **Cancer** (b)	Undisclosed
Cancer (b) **Cancer**		
Bristol-Myers	RAS Famesyl Transferase	RAS FamesylTransferase
Cancer		
Squibb	Inhibitor	Inhibitor
Novartis	MMI 270	MMI 270
Cancer		
Bayer	BAY 12-9566	BAY 12-9566
Cancer		
Merck	Famesyl Transferase Inhibitor	Famesyl Transferase Inhibitor
Cancer (Solid **tumors** - pancreas, colon, **lung**, breast)		
Pfizer	PFE	MMP
Cancer, angiogenesis		
Pfizer	PFE	Tyrosine Kinase

	Cancer, angiogenesis	
Lilly	MTA/LY 231514	MTA/LY 231514
	Cancer Solid **Tumors**	
Lilly	LY 264618/Lometexol	Lometexol
	Cancer Solid **Tumors**	
Scotia	Glamolec	LiGLA (lithium-gamma linolenate)
	Cancer, pancreatic, breast, colon	
Warner Lambert	CI-994	CI-994
	Cancer, Solid **Tumors**/ Leukemia	
Schering AG	Angiogenesis inhibitor	Angiogenesis Inhibitor
	Cancer / Cardio	
Takeda	TNP-470	n/k
	Malignant **Tumor**	
Smithkline Beecham	Hycamtin	Topotecan
	Metastatic Ovarian **Cancer**	
Novartis	PKC 412	PKC 412
	Multi-Drug Resistant **Cancer**	
Novartis	Valspodar	PSC 833
	Myeloid Leukemia/Ovarian **Cancer**	
Immunex	Novantrone	Mitoxantrone
	Pain related to hormone refractory prostate **cancer.**	
Warner Lambert	Metaret	Suramin
	Prostate	
Genentech	Anti-VEGF	Anti-VEGF
	Prostate / Breast / Colorectal / NSCL **Cancer**	
British Biotech	Batimastat	Batimastat (BB94)
	Pterygium	
Eisai	E 7070	E 7070
	Solid **Tumors**	
Biochem Pharma	BCH-4556	BCH-4556
	Solid **Tumors**	
Sankyo	CS-682	CS-682
	Solid **Tumors**	
Agouron	AG2037	AG2037
	Solid **Tumors**	
IDEC Pharma	9-AC	9-AC
	Solid **Tumors**	
Agouron	VEGF/b-FGF Inhibitors	VEGF/b-FGF Inhibitors
	Solid **Tumors**	
Agouron	AG3340	AG3340
	Solid **Tumors** / Macular Degeneration	
Vertex	Incel	VX-710
	Solid **Tumors** - IV	
Vertex	VX-853	VX-853
	Solid **Tumors** - Oral	
Zeneca	ZD 0101 (inj)	ZD 0101
	Solid **Tumors**	
Novartis	ISI 641	ISI 641
	Solid **Tumors**	
Novartis	ODN 698	ODN 698

	Solid **Tumors**	
Tanube Seiyaku	TA 2516	Marimistat
	Solid **Tumors**	
British Biotech	Marimastat	Marimastat (BB 2516)
	Solid **Tumors**	
Celltech	CDP 845	Aggrecanase Inhibitor
	Solid **Tumors** / Breast **Cancer**	
Chiroscience	D2163	D2163
	Solid **Tumors** / Metastases	
Warner Lambert	PD 183805	PD 183805
Daiichi	DX8951f	DX8951f
	Anti-**Cancer**	
Daiichi	Lemonal DP 2202	Lemonal DP 2202
	Anti-**Cancer**	
Fujisawa	FK 317	FK 317
	Anticancer Antibiotic	
Chugai	Picibanil	OK-432
	Antimalignant **Tumor**	
Nycomed	AD 32/valrubicin	Valrubicin
	Bladder **Cancer**-Refractory	
Amersham		
	In situ Carcinoma	
Nycomed	Metastron	Strontium Derivative
	Bone **Cancer** (adjunct	
Amersham		
	therapy, Pain)	
Schering Plough	Temodal	Temozolomide
	Brain **Tumors**	
Schering Plough	Temodal	Temozolonide
	Brain **Tumors**	
Liposome	Evacet	Doxorubicin, Liposomal
	Breast **Cancer**	
Nycomed	Yewtaxan	Paclitaxel
	Breast **Cancer** Advanced,	
Amersham		
	Ovarian **Cancer** Advanced	
Bristol-Myers	Taxol	Paclitaxel
	Breast **Cancer** Advanced,	
Squibb		
	Ovarian **Cancer** Advanced, NSCLC	
Roche	Xeloda	Capecitabine
	Breast **Cancer**, Colorectal **Cancer**	
Roche	Furtulon	Doxifluridine
	Breast **Cancer**, Colorectal **Cancer**, Gastric **Cancer**	
Pharmacia &	Adriamycin	Doxorubicin
	Breast **Cancer**, Leukemia	
Upjohn		
Ivax	Cyclopax	Paclitaxel, Oral
	Breast/Ovarian **Cancer**	
Rhone Poulenc	Oral Taxoid	Oral Taxoid
	Broad **Cancer**	
AHP	Novantrone	Mitoxantrone
	Cancer	
Sequus	SPI-077	Cisplatin, Stealth
	Cancer	

Hoechst	HMR 1275	Flavopiridol
Cancer		
Pfizer	CP-358, 774	EGFR
Cancer		
Pfizer	CP-609, 754	RAS Oncogene Inhibitor
Cancer		
Bristol-Myers	BMS-182751	Oral Platinum
Cancer (**Lung**, Ovarian)		
Squibb		
Bristol-Myers	UFT (Tegafur/Uracil)	UFT (Tegafur/Uracil)
Cancer Oral		
Squibb		
Johnson &	Ergamisol	Levamisole
Cancer Therapy		
Johnson		
Glaxo Welicome	Eniluracil/776C85	5FU Enhancer
Cancer, Refractory Solid & Colorectal **Cancer**		
Johnson &	Ergamisol	Levamisole
Colon **Cancer**		
Johnson		
Rhone Poulenc	Campto	Irinotecan
Colorectal **Cancer**, Cervical **Cancer**		
Pharmacia &	Camptosar	Irinotecan
Colorectal **Cancer**, Cervical		
Upjohn		
Cancer		
Zeneca	Tomudex	Ralitrexed
Colorectal **Cancer**, **Lung Cancer**, Breast **Cancer**		
Johnson &	Leustain	Cladribine
Hairy Cell Leukaemia		
Johnson		
Ivax	Paxene	Paclitaxel
Kaposi Sarcoma		
Segnus	Doxil	Doxorubicin, Liposomal
KS/**Cancer**		
Sequus	Caelyx	Doxorubicin, Liposomal
KS/**Cancer**		
Schering AG	Fludara	Fludarabine
Leukaemia		
Pharmacia &	Pharmorubicin	Epirubicin
Lung/Breast **Cancer**		
Upjohn		
Chiron	DepoCyt	DepoCyt
Neoplastic Meningitis		
Zeneca	ZD1839	ZD 1839
Non Small Cell **Lung Cancer**, Pancreatic **Cancer**		
BASF	LU 79553	Bis-Naphtalimide
Oncology		
BASF	LU 103793	Dolastain
Oncology		
Schering Plough	Caetyx	Doxorubicin-Liposome
Ovarian/Breast **Cancer**		
Lilly	Gemzar	Gemcitabine
Pancreatic **Cancer**, Non Small Cell **Lung Cancer**,		

	Breast, Bladder and Ovarian	
Zeneca	ZD 0473/Anormed	ZD 0473/Anormed
	Platinum based NSCL, ovarian etc.	
Yamanouchi	YM 116	YM 116
	Prostate **Cancer**	
Nycomed	Seeds/I-125 Rapid St	Iodine Seeds
	Prostate **Cancer**	
Amersham		
Agouron	Cdk4/cdk2 inhibitors	cdk4/cdk2 inhibitors
	Solid **Tumors**	
Agouron	PARP inhibitors	PARP Inhibitors
	Solid **Tumors**	
Chiroscience	D4809	Dexifosamide
	Solid **Tumors**	
Bristol-Myers	UFT (Tegafur/Uracil)	UFT (Tegafur/Uracil)
	Solid **Tumors**	
Squibb		
Sankyo	Krestin	Krestin
	Solid **Tumors**	
Asta Medica	Ifex/Mesnex	Ifosamide
	Solid **Tumors**	
Bristol-Myers	Ifex/Mesnex	Ifosamide
	Solid **Tumors**	
Squibb		
Bristol-Myers	Vumon	Teniposide
	Solid **Tumors**	
Squibb		
Bristol-Myers	Paraplatin	Carboplatin
	Solid **Tumors**	
Squibb		
Bristol-Myers	Plantinol	Cisplatin, Stealth
	Solid **Tumors**	
Squibb		
Bristol-Myers	Plantinol	Cisplatin
	Solid **Tumors**	
Squibb		
Bristol-Myers	Vepeside	Etoposide
	Solid **Tumors** Melanoma	
Squibb		
Zeneca	ZD 9331	ZD 9331
	Solid **Tumors**, Advanced Colorectal	
Chugai	Taxotere	Docetaxel
	Solid **Tumors**, Breast **Cancer**	
Rhone Poulenc	Taxotere	Docetaxel
	Solid **Tumors**, Breast **Cancer**	
Glaxo Wellcome	Prodrug of guanine arabinside	prodrug of arabinside
	T Cell Leukemia/Lymphoma & B Cell **Neoplasm**	
Bristol-Myers	Taxane Analog	Taxane Analog
	Taxol follow up	
Squibb		

IT 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 50-76-0, Dactinomycin 50-91-9, Floxuridine 51-21-8, 5-Fluorouracil 52-24-4, Thiotepa 53-19-0, Mitotane 55-86-7, Mechlorethamine hydrochloride 55-98-1, Busulfan 57-22-7, Vincristine 59-05-2, Methotrexate 66-22-8, Uracil, biological studies 69-74-9, Cytarabine hydrochloride 125-84-8, Aminoglutethimide 127-07-1, Hydroxylurea 129-46-4

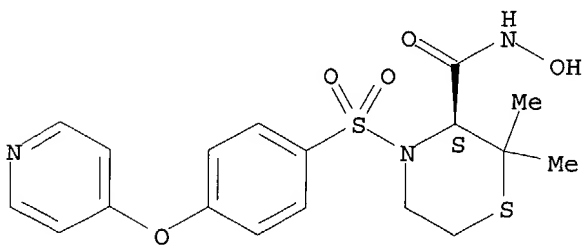
143-67-9, Vinblastine sulfate 145-63-1, Suramin 148-82-3, Melphalan 154-42-7, Thioguanine 154-93-8, Carmustine 305-03-3, Chlorambucil 320-67-2, Azacitidine 366-70-1, Procarbazine hydrochloride 459-86-9, Mitoguazone 555-57-7, Pargyline 645-05-6, Hexamethylmelamine 1605-68-1D, Taxane, analogs 3094-09-5, Furtulon 3778-73-2, Ifosfamide 4291-63-8, Leustatin 4342-03-4, Dacarbazine 7440-24-6D, Strontium, derivs. 9015-68-3, Asparaginase 11056-06-7, Bleomycin 11096-26-7, Erythropoietin 13010-20-3D, Nitrosourea, derivs. 13010-47-4, Lomustine 13311-84-7, Flutamide 13909-09-6, Semustine 14769-73-4 15663-27-1 17902-23-7, Tegafur 18378-89-7, Plicamycin 18883-66-4, Streptozocin 19767-45-4, Mesnex 23214-92-8 23541-50-6, Daunorubicin hydrochloride 25191-14-4, Poly(G) 25316-40-9, Adriamycin 29767-20-2, Vumon 31441-78-8, Mercaptopurine 33069-62-4 33419-42-0 38270-90-5, Metastron 39325-01-4, Picibanil 41575-94-4, Paraplatin 51264-14-3, Amsacrine 52205-73-9, Estramustine phosphate sodium 53910-25-1, Pentostatin 54965-24-1, Tamoxifen citrate 56124-62-0, Valrubicin 59917-39-4, Vindesine sulfate 59989-18-3, Eniluracil 66849-34-1, Dexifosfamide 70476-82-3, Novantrone 74381-53-6, Leuprolide acetate 74578-38-4, UFT 77907-69-8, Interferon alfa-2a 83150-76-9, Octreotide 83869-56-1, GM-CSF 85622-93-1, Temozolomide 90409-78-2, Polifeprosan 91421-43-1, 9-Aminocamptothecin 95058-81-4, Gemcitabine 97682-44-5, Camptosar 98530-12-2, Interferon alfa-2b 100286-90-6, Campto 102409-92-7, FK 317 106400-18-4, LY 264618 106400-81-1, Lometrexol 112522-64-2, CI-994 112887-68-0, Raltitrexed 114977-28-5, Taxotere 119413-54-6, Hycamtin 119876-18-5 120685-11-2, PKC412 121584-18-7, Valspodar 122051-95-0 122111-03-9, Gemzar 123948-87-8, Topotecan 129298-91-5, TNP-470 129580-63-8, BMS 182751 130370-60-4, Batimastat 141907-41-7, Matrix metalloproteinase 145918-75-8, BCH-4556 146426-40-6, HMR 1275 150399-23-8, LY231514 151823-14-2, CS-682 153537-73-6, ZD 9331 154039-60-8 154361-50-9, Capecitabine 159776-69-9, LU 103793 159997-94-1 162706-37-8, LU 79553 165668-41-7, E7070 169799-04-6 169869-90-3, DX8951f 174722-31-7, Rituximab 179545-77-8, BAY 12-9566 181630-15-9, ZD 0473 183012-14-8, YM 116 183319-69-9, CP 358774 184046-91-1 190454-58-1, VX-853 **192329-42-3**, AG3340 209164-46-5, CDP 845 209973-83-1, BLP 25 213327-37-8, OvaRex 259188-38-0, D 2163 289499-45-2, PD 183805 340014-19-9, Melacine 386211-12-7, AG 3433 386211-13-8, ZD 0101 386211-20-7, ISI 641 386211-21-8, ODN 698 386211-47-8, Lemonal DP 2202 386211-48-9, CP 609754
(immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

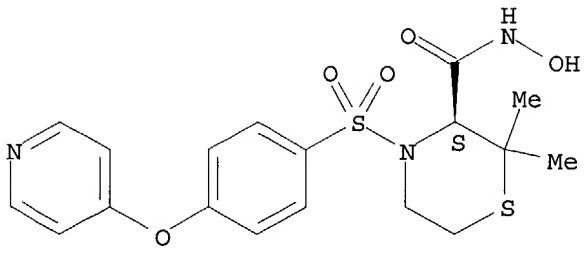
IT **192329-42-3**, AG3340
(immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

RN 192329-42-3 USPATFULL

CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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L1              STR
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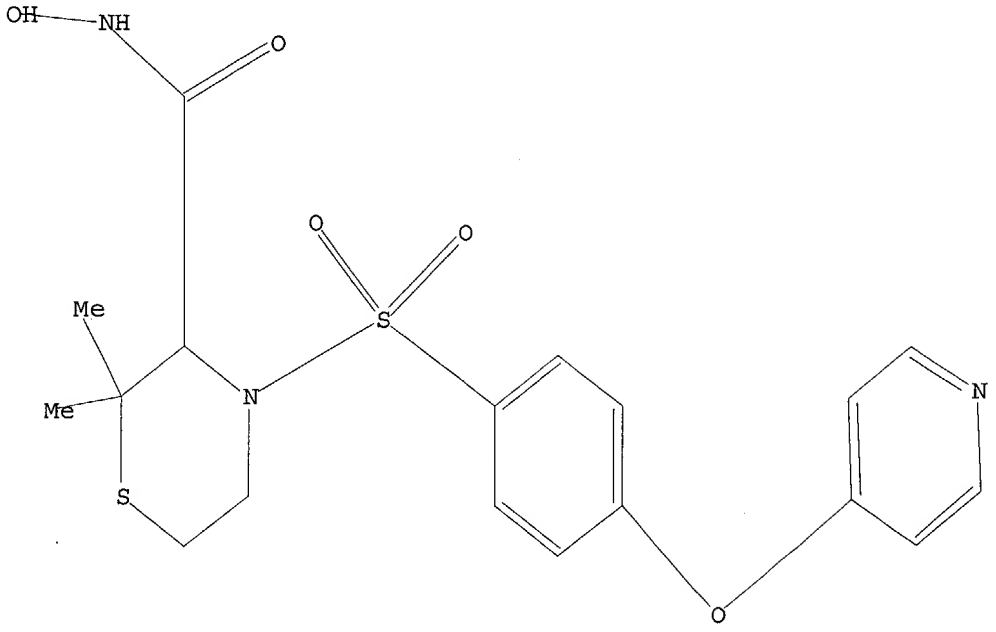


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Structure attributes must be viewed using STN Express query preparation.


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SAMPLE SEARCH INITIATED 21:16:44 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      1 TO ITERATE

100.0% PROCESSED       1 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO       80
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 21:16:50 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     33 TO ITERATE

100.0% PROCESSED      33 ITERATIONS                                8 ANSWERS
SEARCH TIME: 00.00.01

L3            8 SEA SSS FUL L1
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09/857,876

```
> d his

     (FILE 'HOME' ENTERED AT 21:15:45 ON 23 DEC 2003)

     FILE 'REGISTRY' ENTERED AT 21:16:20 ON 23 DEC 2003
L1                STRUCTURE UPLOADED
L2              0 S L1 SSS SAM
L3              8 S L1 SSS FULL

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 21:17:00 ON 23 DEC 2003
L4             84 S L3
L5             31 S L4 AND LUNG(P)(CANCER? OR TUMOR? OR TUMOUR? OR NEOPLAS?)
L6             30 DUP REM L5 (1 DUPLICATE REMOVED)
L7              5 S L6 AND RADIAT?

     FILE 'STNGUIDE' ENTERED AT 21:20:26 ON 23 DEC 2003

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 21:23:04 ON 23 DEC 2003

     FILE 'STNGUIDE' ENTERED AT 21:23:07 ON 23 DEC 2003

     FILE 'STNGUIDE' ENTERED AT 21:23:20 ON 23 DEC 2003

     FILE 'STNGUIDE' ENTERED AT 21:30:57 ON 23 DEC 2003

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 21:32:24 ON 23 DEC 2003
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09/857,876

=> file hcaplus, uspatfull

FILE 'HCAPLUS' ENTERED AT 21:32:24 ON 23 DEC 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'USPATFULL' ENTERED AT 21:32:24 ON 23 DEC 2003

=> d l6 abs ibib kwic hitstr 10, 14, 17, 22, 28-30

L6 ANSWER 10 OF 30 USPATFULL on STN

AB The invention relates to compounds of the formula 1: ##STR1##

wherein: Z is O or S; V is a divalent radical which together with C* and N forms a ring having six ring atoms, where each of said ring atoms other than C* and N independently is unsubstituted or substituted by a suitable substituent, and at least one of said other ring atoms is a heteroatom selected from O, N and S, and the remainder are carbon atoms; and Ar is an aryl or heteroaryl group; and pharmaceutically acceptable prodrugs, salts and solvates thereof.

The invention further relates to pharmaceutically acceptable prodrugs, salts and solvates of these compounds. The invention also relates to methods of inhibiting the activity of metalloproteinases by administering a compound of the formula I or a prodrug, salt of solvate thereof. The invention further relates to pharmaceutical compositions comprising an effective amount of these compounds, prodrugs, salts, and solvates. The invention still further relates to methods and intermediates useful for preparing these compounds, prodrugs, salts, and solvates.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:188713 USPATFULL
TITLE:	Metalloproteinase inhibitors, pharmaceutical compositions containing them and their pharmaceutical uses, and methods and intermediates useful for their preparation
INVENTOR(S):	Zook, Scott E., Del Mar, CA, UNITED STATES Dagnino, Raymond, JR., San Diego, CA, UNITED STATES Deason, Michael E., Poway, CA, UNITED STATES Bender, Steven L., Oceanside, CA, UNITED STATES Melnick, Michael J., San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S):	Agouron Pharmaceuticals, Inc., San Diego, CA, UNITED STATES, 92121 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003130506	A1	20030710
APPLICATION INFO.:	US 2002-298842	A1	20021118 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-675555, filed on 29 Sep 2000, GRANTED, Pat. No. US 6500948 Division of Ser. No. US 1998-11971, filed on 29 Jun 1998, GRANTED, Pat. No. US 6153757 A 371 of International Ser. No. WO 1996-US19328, filed on 5 Dec 1996, PENDING A 371 of International Ser. No. US 1996-759713, filed on 6 Dec 1996, GRANTED, Pat. No. US 5753653

NUMBER	DATE

PRIORITY INFORMATION:	US 1995-41496P 19951208 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	FITZPATRICK CELLA HARPER & SCINTO, 30 ROCKEFELLER PLAZA, NEW YORK, NY, 10112
NUMBER OF CLAIMS:	89
EXEMPLARY CLAIM:	1
LINE COUNT:	4100

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0504] Primary subcutaneous **tumors** were established in female BDF.sub.1 mice by trocar inoculation of the murine Lewis **lung** carcinoma (NIH) **tumor** line. This **tumor** line produces spontaneous **lung** metastases which arise from the primary **tumor**. Primary **tumor** growth was monitored by measuring the length and width of the subcutaneous **tumor** using calipers; **lung** metastases were counted at the end of the experiment (22 days after **tumor** implantation) by removing the lungs and counting the lesions using a dissecting microscope. The test compound was administered daily, i.p., beginning 24 hours after **tumor** implantation (day 1) and continuing through day 21. Primary **tumor** volumes and number of **lung** metastases were compared to control animals using an ANOVA followed by a comparison of means using the F statistic. For example, the compound of Example 9(a), at a dosage of 50 mg/kg, produced a statistically significant ($p<0.025$) **tumor** growth delay, calculated as the delay in reaching 1000 mm.sup.3 **tumor** volume between control and treated animals, and in the number of **lung** metastases ($p<0.05$) relative to the control. All drugs were administered at 50 mg/kg, i.p., daily, Day 1-Day 21. The results are presented in Table 2 below.

TABLE 2

Example No.	**Tumor** Growth Delay	% Inhibition-**Lung** Metastases
5(a)	2.0 days	13.6%
8(a)	-0.1 days	7.5%
7(a)	0.0 days	16.1%
9(a)	7.2 days ($p < 0.025$)	77.6% ($p < 0.05$)

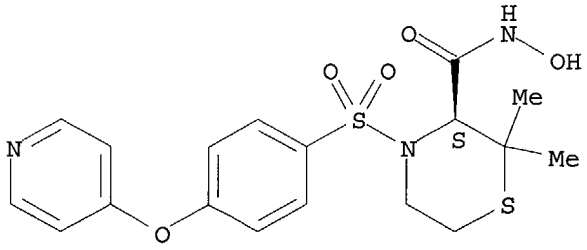
IT **192329-42-3P** 192329-43-4P 192329-45-6P 192329-46-7P
192329-47-8P 192329-48-9P 192329-49-0P 192329-50-3P 192329-51-4P
192329-53-6P 192329-54-7P 192329-55-8P 192329-56-9P 192329-57-0P
192329-58-1P 192329-59-2P 192329-60-5P 192329-61-6P
192329-63-8P 192329-65-0P 192329-68-3P 192329-69-4P 192329-70-7P
192329-71-8P 192329-73-0P 192329-74-1P 192329-75-2P 192329-76-3P
192329-77-4P 192329-78-5P 192329-95-6P 192329-98-9P 192330-14-6P
192330-15-7P 192330-16-8P 192330-17-9P 192330-18-0P 192330-19-1P
192330-20-4P 192330-21-5P 192330-22-6P 192330-27-1P 192330-28-2P
192330-33-9P 192330-37-3P 192330-52-2P **192330-53-3P**
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

IT **192329-42-3P 192329-58-1P 192330-53-3P**
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

RN 192329-42-3 USPATFULL

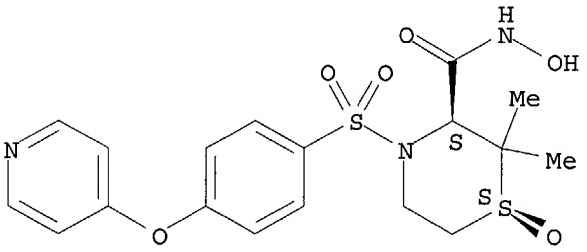
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



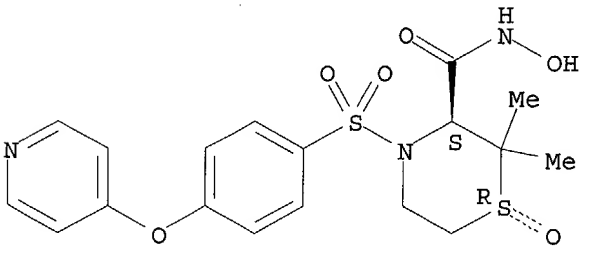
RN 192329-58-1 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1S,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 192330-53-3 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1R,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 14 OF 30 USPATFULL on STN
AB The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of radiation therapy and a cyclooxygenase-2 inhibitor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:302884 USPATFULL
TITLE: Combination therapy of radiation and a COX-2 inhibitor for treatment of neoplasia
INVENTOR(S): McKearn, John P, St. Louis, MO, United States
Masferrer, Jaime L, Ballwin, MO, United States

PATENT ASSIGNEE(S):	Milas, Luka, Houston, TX, United States Pharmacia Corporation, St. Louis, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6649645	B1	20031118
APPLICATION INFO.:	US 1999-385214		19990827 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-113786P	19981223 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Criares, Theodore J.
ASSISTANT EXAMINER:	Kim, Jennifer
LEGAL REPRESENTATIVE:	Bulock, Joseph W., Warner, James M.
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT:	1434

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of breast, **lung**, and testicular **cancer**.

DETD In one embodiment of the invention a method for treating **neoplasia** in a subject in need of such treatment comprises treating the subject with radiation therapy and a therapeutically effective amount of a cyclooxygenase-2 inhibitor or pharmaceutically acceptable salt or derivative thereof wherein the **neoplasia** is selected from **lung cancer**, breast **cancer**, gastrointestinal **cancer**, bladder **cancer**, head and neck **cancer**, and cervical **cancer**.

DETD **Lung Cancer**

DETD In many countries including Japan, Europe and America, the number of patients with **lung cancer** is fairly large and continues to increase year after year and is the most frequent cause of **cancer** death in both men and women. Although there are many potential causes for **lung cancer**, tobacco use, and particularly cigarette smoking, is the most important. Additionally, etiologic factors such as exposure to asbestos, especially in. . . identified as an important factor. Finally, genetic factors have also been identified as another factor that increase the risk of **cancer**.

DETD **Lung cancers** can be histologically classified into non-small cell **lung cancers** (e.g. squamous cell carcinoma (epidermoid), adenocarcinoma, large cell carcinoma (large cell anaplastic), etc.) and small cell **lung cancer** (oat cell). Non-small cell **lung cancer** (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell **lung cancer** (SCLC). Thus, chemotherapeutic formulas and radiation therapy are different between these two types of **lung cancer**.

DETD Non-Small Cell **Lung Cancer**

DETD Where the location of the non-small cell **lung cancer** **tumor** can be easily excised (stage I and II disease) surgery is the first line of therapy and offers a relatively good chance for a cure. However, in more advanced disease (stage IIIa and greater), where the **tumor** has extended to tissue beyond the bronchopulmonary

lymph nodes, surgery may not lead to complete excision of the **tumor**. In such cases, the patient's chance for a cure by surgery alone is greatly diminished. Where surgery will not provide complete removal of the NSCLC **tumor**, other types of therapies must be utilized.

DETD It is reported that advanced non-small cell **lung cancers** do not respond favorably to single-agent chemotherapy and useful therapies for advanced inoperable **cancers** have been limited. (J. Clin. Oncol. 1992, 10, 829-838).

DETD . . . macrolide antibiotics as a drug delivery carrier capable of transporting anthoracycline-type anticancer drugs into the lungs for the treatment of **lung cancers**. However, the macrolide antibiotics specified herein are disclosed to be only a drug carrier, and there is no reference to the therapeutic use of macrolides against non-small cell **lung cancers**.

DETD WO 93/18652 refers to the effectiveness of the specified 16-membered-ring macrolides such as bafilomycin, etc. in treating non-small cell **lung cancers**, but they have not yet been clinically practicable.

DETD . . . which contribute to host immune responses, but there is no reference to the effect of this drug on non-small cell **lung cancers**.

DETD . . . of antimicrobial drugs can be used as an anticancer agent, but does not refer to their application to non-small cell **lung cancers**.

DETD . . . addition, interleukins are known to have an antitumor effect, but have not been reported to be effective against non-small cell **lung cancers**.

DETD Any 14- or 15-membered-ring macrolides have not been reported to be effective against non-small cell **lung cancers**.

DETD Small Cell **Lung Cancer**

DETD Approximately 15 to 20 percent of all cases of **lung cancer** reported worldwide is small cell **lung cancer** (SCLC). (Ihde, **Cancer** 1984, 54, 2722). Currently, treatment of SCLC incorporates multi-modal therapy, including chemotherapy, radiation therapy and surgery. Response rates of localized or disseminated SCLC remain high to systemic chemotherapy, however, persistence of the primary **tumor** and persistence of the **tumor** in the associated lymph nodes has led to the integration of several therapeutic modalities in the treatment of SCLC.

CLM What is claimed is:

2. The method of claim 1 wherein the **neoplasia** is selected from the group consisting of **lung cancer**; breast **cancer**; gastrointestinal **cancer**; bladder **cancer**; head and neck **cancer**; cervical **cancer** ; colorectal **cancer**; prostate **cancer**; and pancreatic **cancer**.

3. The method of claim 2 wherein the **neoplasia** is **lung cancer**.

IT 50-18-0, Cyclophosphamide 51-21-8, Fluorouracil 52-24-4, Thiotepa 53-86-1, Indomethacin 57-22-7, Vincristine 58-05-9, Leucovorin 76-43-7, Fluoxymesterone 128-13-2, Ursodeoxycholic acid 302-79-4, Retinoic acid 471-34-1, Calcium carbonate, biological studies 865-21-4, Vinblastine 1464-42-2, Selenomethionine 3562-63-8, Megestrol 7782-49-2, Selenium, biological studies 10540-29-1, Tamoxifen 14769-73-4, Levamisole 15663-27-1, Cisplatin 15866-90-7 23214-92-8, Doxorubicin 33069-62-4, Paclitaxel 33419-42-0, Etoposide

41575-94-4, Carboplatin 51803-78-2 59973-80-7, Sulindac sulfone
65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 65807-02-5,
Goserelin 70052-12-9, Eflornithine 71486-22-1, Vinorelbine
80937-31-1 84449-90-1, Raloxifene 89778-26-7, Toremifene 93014-16-5
95058-81-4, Gemcitabine 97682-44-5, Irinotecan 107868-30-4,
Exemestane 112809-51-5, Letrozole 114977-28-5, Docetaxel
120511-73-1, Anastrozole 123653-11-2 123663-49-0 123948-87-8,
Topotecan 154039-60-8 154361-50-9, Capecitabine 158205-05-1
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Celecoxib 170569-86-5 170569-87-6 170569-88-7 170630-40-7
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[1,1':2',1''-Terphenyl]-4-sulfonamide 179382-91-3 179545-77-8
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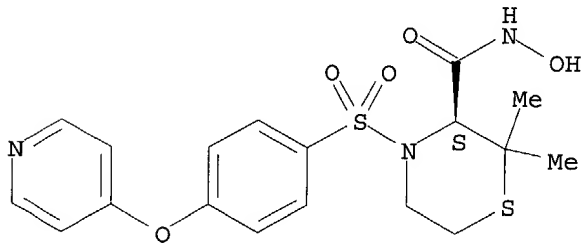
279221-25-9 279221-26-0 279221-27-1 279221-28-2
(cyclooxygenase-2 inhibitor and matrix metalloproteinase inhibitor in combination therapy for neoplasia treatment)

IT **192329-42-3**
(cyclooxygenase-2 inhibitor and matrix metalloproteinase inhibitor in combination therapy for neoplasia treatment)

RN 192329-42-3 USPATFULL

CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 17 OF 30 USPATFULL on STN

AB The invention relates to compounds of the formula 1: ##STR1##

wherein: Z is O or S; V is a divalent radical which together with C* and N forms a ring having six ring atoms, where each of said ring atoms other than C* and N independently is unsubstituted or substituted by a suitable substituent, and at least one of said other ring atoms is a heteroatom selected from O, N and S, and the remainder are carbon atoms; and Ar is an aryl or heteroaryl group; and pharmaceutically acceptable prodrugs, salts and solvates thereof.

The invention further relates to pharmaceutically acceptable prodrugs, salts and solvates of these compounds. The invention also relates to

methods of inhibiting the activity of metalloproteinases by administering a compound of the formula I or a prodrug, salt of solvate thereof. The invention further relates to pharmaceutical compositions comprising an effective amount of these compounds, prodrugs, salts, and solvates. The invention still further relates to methods and intermediates useful for preparing these compounds, prodrugs, salts, and solvates.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:346986 USPATFULL
TITLE:	Metalloproteinase inhibitors-compositions, uses preparation and intermediates thereof
INVENTOR(S):	Zook, Scott E., Del Mar, CA, United States Dagnino, Jr., Raymond, San Diego, CA, United States Deason, Michael E., Poway, CA, United States Bender, Steven L., Oceanside, CA, United States Melnick, Michael J., San Diego, CA, United States
PATENT ASSIGNEE(S):	Agouron Pharmaceuticals, Inc., La Jolla, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6500948	B1	20021231
APPLICATION INFO.:	US 2000-675555		20000929 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 11971, now patented, Pat. No. US 6153757 Division of Ser. No. US 675555 Continuation-in-part of Ser. No. US 1996-759713, filed on 6 Dec 1996, now patented, Pat. No. US 5753653

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-41496P	19951208 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Raymond, Richard L.
ASSISTANT EXAMINER:	Truong, Tamthom N.
LEGAL REPRESENTATIVE:	Fitzpatrick, Cella, Harper & Scinto LLP
NUMBER OF CLAIMS:	35
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:	4123

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Primary subcutaneous **tumors** were established in female BDF.sub.1 mice by trocar innoculation of the murine Lewis **lung** carcinoma (NIH) **tumor** line. This **tumor** line produces spontaneous **lung** metastases which arise from the primary **tumor**. Primary **tumor** growth was monitored by measuring the length and width of the subcutaneous **tumor** using calipers; **lung** metastases were counted at the end of the experiment (22 days after **tumor** implantation) by removing the lungs and counting the lesions using a dissecting microscope. The test compound was administered daily, i.p., beginning 24 hours after **tumor** implantation (day 1) and continuing through day 21. Primary **tumor** volumes and number of **lung** metastases were compared to control animals using an ANOVA followed by a comparison of means using the F statistic. For example, the compound of example 9(a), at a dosage of 50 mg/kg, produced a statistically significant ($p<0.025$) **tumor** growth delay, calculated as the delay in reaching 1000 mm.sup.3 **tumor** volume between control and treated animals, and

in the number of **lung** metastases ($p<0.05$) relative to the control. All drugs were administered at 50 mg/kg, i.p., daily, Day 1-Day 21. The results. . .

DETD
TABLE 2

Example No. **Tumor** Growth Delay % Inhibition-**Lung** Metastases

5(a) 2.0 days 13.6%
8(a) -0.1 days 7.5%
7(a) 0.0 days 16.1%
9(a) 7.2 days ($p < 0.025$) 77.6% ($p < 0.05$)

IT **192329-42-3P** 192329-43-4P 192329-45-6P 192329-46-7P
192329-47-8P 192329-48-9P 192329-49-0P 192329-50-3P 192329-51-4P
192329-53-6P 192329-54-7P 192329-55-8P 192329-56-9P 192329-57-0P
192329-58-1P 192329-59-2P 192329-60-5P 192329-61-6P
192329-63-8P 192329-65-0P 192329-68-3P 192329-69-4P 192329-70-7P
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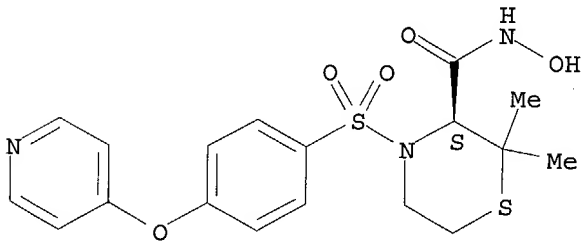
192330-20-4P 192330-21-5P 192330-22-6P 192330-27-1P 192330-28-2P
192330-33-9P 192330-37-3P 192330-52-2P **192330-53-3P**
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

IT **192329-42-3P 192329-58-1P 192330-53-3P**
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

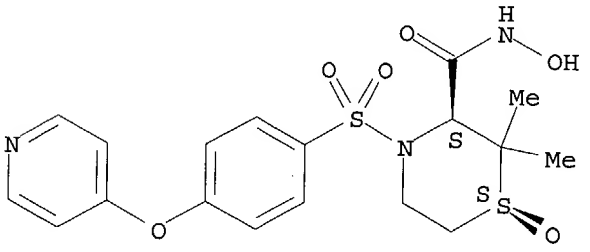
RN 192329-42-3 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

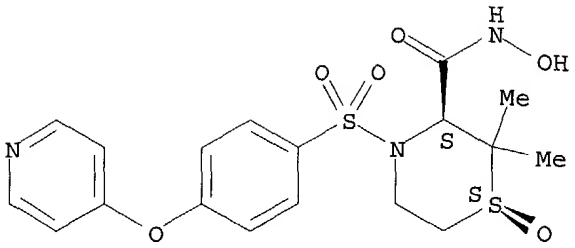
Absolute stereochemistry.



RN 192329-58-1 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1S,3S)- (9CI) (CA INDEX NAME)

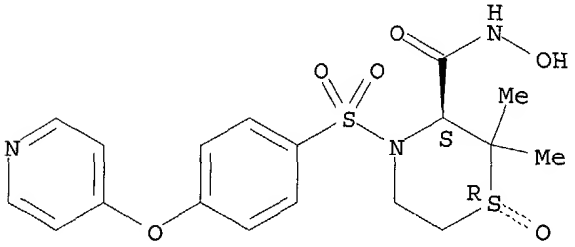
Absolute stereochemistry.





RN 192330-53-3 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1R,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 22 OF 30 USPATFULL on STN
AB The invention relates to compounds of formula (1) ##STR1## wherein: Z is O or S; V is a divalent radical which together with C* and N forms a ring having six ring atoms, where each of said ring atoms other than C* and N independently is unsubstituted or substituted by a suitable substituent, and at least one of said other ring atoms is a heteroatom selected from O, N and S, and the remainder is carbon atoms; and Ar is an aryl or heteroaryl group; and pharmaceutically acceptable prodrugs, salts and solvates thereof. The invention further relates to pharmaceutically acceptable prodrugs, salts and solvates of these compounds. The invention also relates to methods of inhibiting the activity of metalloproteinases by administering a compound of formula (1) or a prodrug, salt or solvate thereof. The invention further relates to pharmaceutical compositions comprising an effective amount of these compounds, prodrugs, salts, and solvates. The invention still further relates to methods and intermediates useful for preparing these compounds, prodrugs, salts, and solvates.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:161153 USPATFULL
TITLE:	Metalloproteinase inhibitors and intermediates useful for their preparation
INVENTOR(S):	Zook, Scott E., Del Mar, CA, United States Dagnino, Jr., Raymond, San Diego, CA, United States Deason, Michael E., Poway, CA, United States Bender, Steven L., Oceanside, CA, United States Melnick, Michael J., San Diego, CA, United States
PATENT ASSIGNEE(S):	Agouron Pharmaceuticals, Inc., La Jolla, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6153757		20001128	
	~~WO 9720824~~		19970612	
APPLICATION INFO.:	US 1998-11971		19980629	(9)
	WO 1996-US19328		19961205	
			19980629	PCT 371 date
			19980629	PCT 102(e) date

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-759713, filed on 6 Dec 1996, now patented, Pat. No. US 5753653

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-41496P	19951208 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 3755
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Primary subcutaneous **tumors** were established in female BDF.sub.1 mice by trocar innoculation of the murine Lewis **lung** carcinoma (NIH) **tumor** line. This **tumor** line produces spontaneous **lung** metastases which arise from the primary **tumor**. Primary **tumor** growth was monitored by measuring the length and width of the subcutaneous **tumor** using calipers; **lung** metastases were counted at the end of the experiment (22 days after **tumor** implantation) by removing the lungs and counting the lesions using a dissecting microscope. The test compound was administered daily, i.p., beginning 24 hours after **tumor** implantation (day 1) and continuing through day 21. Primary **tumor** volumes and number of **lung** metastases were compared to control animals using an ANOVA followed by a comparison of means using the F statistic. For example, the compound of example 9(a), at a dosage of 50 mg/kg, produced a statistically significant ($p<0.025$) **tumor** growth delay, calculated as the delay in reaching 1000 mm.sup.3 **tumor** volume between control and treated animals, and in the number of **lung** metastases ($p<0.05$) relative to the control. All drugs were administered at 50 mg/kg, i.p., daily, Day 1-Day 21. The results. . .

DETD TABLE 2

Example No.	**Tumor** Growth Delay	% Inhibition-**Lung** Metastases
5(a)	2.0 days	13.6%
8(a)	-0.1 days	7.5%
7(a)	0.0 days	16.1%
9(a)	7.2 days ($p < 0.025$)	77.6% ($p < 0.05$)

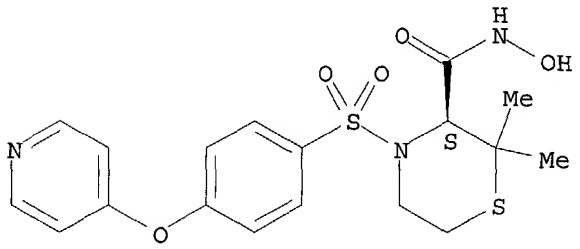
IT **192329-42-3P** 192329-43-4P 192329-45-6P 192329-46-7P
192329-47-8P 192329-48-9P 192329-49-0P 192329-50-3P 192329-51-4P
192329-53-6P 192329-54-7P 192329-55-8P 192329-56-9P 192329-57-0P
192329-58-1P 192329-59-2P 192329-60-5P 192329-61-6P
192329-63-8P 192329-65-0P 192329-68-3P 192329-69-4P 192329-70-7P
192329-71-8P 192329-73-0P 192329-74-1P 192329-75-2P 192329-76-3P

192329-77-4P 192329-78-5P 192329-95-6P 192329-98-9P 192330-14-6P
192330-15-7P 192330-16-8P 192330-17-9P 192330-18-0P 192330-19-1P
192330-20-4P 192330-21-5P 192330-22-6P 192330-27-1P 192330-28-2P
192330-33-9P 192330-37-3P 192330-52-2P **192330-53-3P**
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

IT **192329-42-3P 192329-58-1P 192330-53-3P**
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

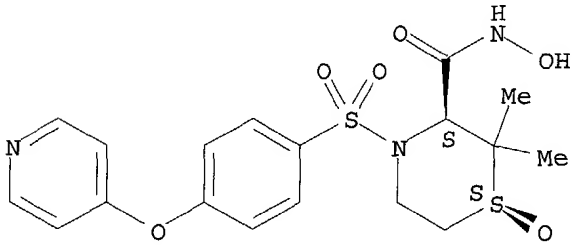
RN 192329-42-3 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



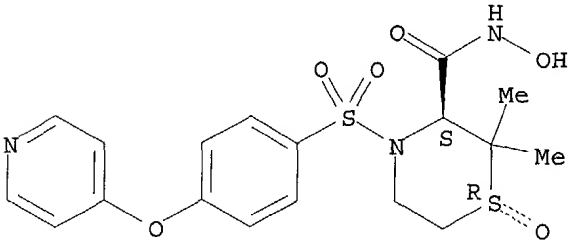
RN 192329-58-1 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1S,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 192330-53-3 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1R,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 28 OF 30 USPATFULL on STN

AB The invention relates to compounds of the formula I ##STR1## in which Q is a divalent radical having four ring atoms which together with C* and N form a six-membered ring, each of these four ring atoms being unsubstituted or substituted by a suitable substituent and at least one being a heteroatom selected from O, N and S, with the remainder being carbon atoms; and Ar is an aryl or heteroaryl group. The invention further relates to pharmaceutically acceptable prodrugs and pharmaceutically acceptable salts of these compounds. The invention also relates to methods of inhibiting the activity of metalloproteinases, especially MMPs or TNF-.alpha., by administering a compound of the formula I or a salt or prodrug thereof. The invention further relates to pharmaceutical compositions comprising an effective amount of these compounds, salts, and prodrugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:54896 USPATFULL
TITLE: Metalloproteinase inhibitors, pharmaceutical compositions containing them and their pharmaceutical uses
INVENTOR(S): Bender, Steven L., Oceanside, CA, United States
Melnick, Michael J., San Diego, CA, United States
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., LaJolla, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5753653		19980519
APPLICATION INFO.:	US 1996-759713		19961206 (8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-41496P	19951208 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Grumbling, Matthew V.
LEGAL REPRESENTATIVE: Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 2238

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Primary subcutaneous **tumors** were established in female BDF, mice by trocar innoculation of the murine Lewis **lung** carcinoma (NIH) **tumor** line. This **tumor** line produces spontaneous **lung** metastases which arise from the primary **tumor**. Primary **tumor** growth was monitored by measuring the length and width of the subcutaneous **tumor** using calipers; **lung** metastases were counted at the end of the experiment (22 days after **tumor** implantation) by removing the lungs and counting the lesions using a dissecting microscope. The test compound was administered daily, i.p., beginning 24 hours after **tumor** implantation (day 1) and continuing through day 21. Primary **tumor** volumes and number of **lung** metastases were compared to control animals using an ANOVA followed by a comparison of means using the F statistic. For example, the compound of example 9(a), at a dosage of 50 mg/kg, produced a statistically significant ($p<0.025$) **tumor** growth delay, calculated as the delay in reaching 1000 mm.sup.3 **tumor** volume between control and treated animals, and

in the number of **lung** metastases ($p<0.05$) relative to the control. All drugs were administered at 50 mg/kg, i.p., daily, Day 1-Day 21. The results. . .

DETD TABLE 2

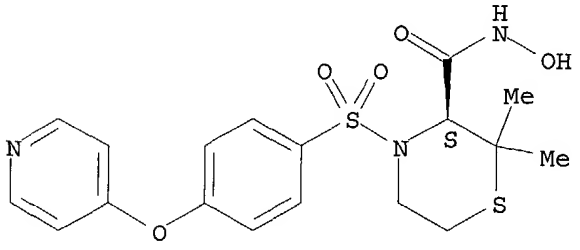
Example No.	**Tumor** Growth Delay	% Inhibition of **Lung** Metastases
5(a)	2.0 days	13.6%
8(a)	-0.1 days	7.5%
7(a)	0.0 days	16.1%
9(a)	7.2 days ($p < 0.025$)	77.6% ($p < 0.05$)

IT **192329-42-3P** 192329-44-5P 192329-45-6P 192329-46-7P
192329-47-8P 192329-48-9P 192329-49-0P 192329-50-3P 192329-51-4P
192329-52-5P 192329-53-6P 192329-54-7P 192329-55-8P 192329-56-9P
192329-57-0P 192329-79-6P 192329-98-9P 192330-14-6P 192330-15-7P
192330-17-9P 192330-18-0P 192330-19-1P 192330-20-4P 192330-21-5P
192330-27-1P 192330-28-2P 192330-33-9P 192330-37-3P 192330-51-1P
207795-08-2P 207795-09-3P 207795-10-6P 207795-11-7P 207795-12-8P
207795-13-9P 207795-14-0P 207795-15-1P **207795-16-2P**
(prepn. of N-hydroxy-1-arylsulfonylazine-2-carboxamides and analogs as metalloproteinase inhibitors)

IT **192329-42-3P 207795-16-2P**
(prepn. of N-hydroxy-1-arylsulfonylazine-2-carboxamides and analogs as metalloproteinase inhibitors)

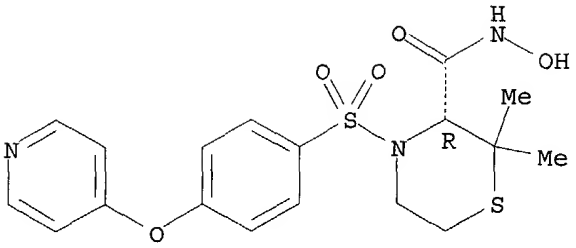
RN 192329-42-3 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 207795-16-2 USPATFULL
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 29 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
GI For diagram(s), see printed CA Issue.
AB The title compds [I; Z = O, S; V = divalent radical which together with chiral carbon, C*, and N and forms an (un)substituted heterocyclic ring having six ring atoms; A = (un)substituted aryl or heteroaryl], useful as metalloproteinase inhibitors for the treatment of **cancer** or arthritis, are prepd. Thus, 2(R)-N-hydroxy-1-[4-(4-chlorophenoxy)benzenesulfonyl]-4-(tert-butoxycarbonyl)piperazine-2-carboxamide (m.p. 94.6.degree.), prepd. from 2(R)-piperazine-2-carboxylic acid in 4 steps, demonstrated a 77.6% inhibition of **lung** metastases in a female mouse Lewis **lung** carcinoma model at 50 mg/kg (i.p.).

ACCESSION NUMBER: 1997:496833 HCAPLUS
DOCUMENT NUMBER: 127:108945
TITLE: Preparation of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics
INVENTOR(S): Zook, Scott E.; Dagnino, Raymond Jr.; Deason, Michael E.; Bender, Steven L.; Melnick, Michael J.
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA; Zook, Scott E.; Dagnino, Raymond Jr.; Deason, Michael E.; Bender, Steven L.; Melnick, Michael J.
SOURCE: PCT Int. Appl., 150 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9720824	A1	19970612	WO 1996-US19328	19961205
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238306	AA	19970612	CA 1996-2238306	19961205
AU 9714091	A1	19970627	AU 1997-14091	19961205
AU 725831	B2	20001019		
EP 874830	A1	19981104	EP 1996-944229	19961205
EP 874830	B1	20030312		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1207734	A	19990210	CN 1996-199583	19961205

BR 9611929	A	19990518	BR 1996-11929	19961205
NZ 325559	A	20000128	NZ 1996-325559	19961205
JP 2000502330	T2	20000229	JP 1997-521405	19961205
EP 1095936	A1	20010502	EP 2000-128719	19961205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 234291	E	20030315	AT 1996-944229	19961205
PT 874830	T	20030630	PT 1996-96944229	19961205
ZA 9704954	A	19990105	ZA 1997-4954	19970605
NO 9802590	A	19980805	NO 1998-2590	19980605
US 6153757	A	20001128	US 1998-11971	19980629
US 6500948	B1	20021231	US 2000-675555	20000929
US 2003130506	A1	20030710	US 2002-298842	20021118

PRIORITY APPLN. INFO.:

US 1995-569766	A2	19951208
US 1995-41496P	P	19951208
EP 1996-944229	A3	19961205
WO 1996-US19328	W	19961205
US 1996-759713	A2	19961206
US 1998-11971	A3	19980629
US 2000-675555	A3	20000929

OTHER SOURCE(S): MARPAT 127:108945

AB . . . heterocyclic ring having six ring atoms; A = (un)substituted aryl or heteroaryl], useful as metalloproteinase inhibitors for the treatment of **cancer** or arthritis, are prepd. Thus, 2(R)-N-hydroxy-1-[4-(4-chlorophenoxy)benzenesulfonyl]-4-(tert-butoxycarbonyl)piperazine-2-carboxamide (m.p. 94.6.degree.), prepd. from 2(R)-piperazine-2-carboxylic acid in 4 steps, demonstrated a 77.6% inhibition of **lung** metastases in a female mouse Lewis **lung** carcinoma model at 50 mg/kg (i.p.).

IT **192329-42-3P** 192329-43-4P 192329-45-6P 192329-46-7P
192329-47-8P 192329-48-9P 192329-49-0P 192329-50-3P 192329-51-4P
192329-53-6P 192329-54-7P 192329-55-8P 192329-56-9P 192329-57-0P
192329-58-1P 192329-59-2P 192329-60-5P 192329-61-6P
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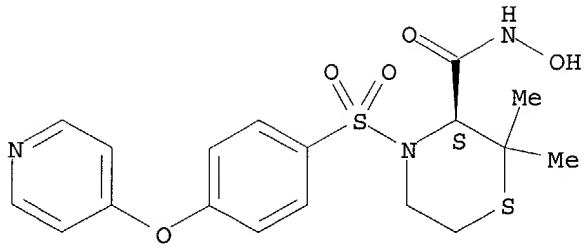
192329-71-8P 192329-73-0P 192329-74-1P 192329-75-2P 192329-76-3P
192329-77-4P 192329-78-5P 192329-95-6P 192329-98-9P 192330-14-6P
192330-15-7P 192330-16-8P 192330-17-9P 192330-18-0P 192330-19-1P
192330-20-4P 192330-21-5P 192330-22-6P 192330-27-1P 192330-28-2P
192330-33-9P 192330-37-3P 192330-52-2P **192330-53-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

IT **192329-42-3P 192329-58-1P 192330-53-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic metalloproteinase-inhibitor antitumor agents and antiarthritics)

RN 192329-42-3 HCAPLUS

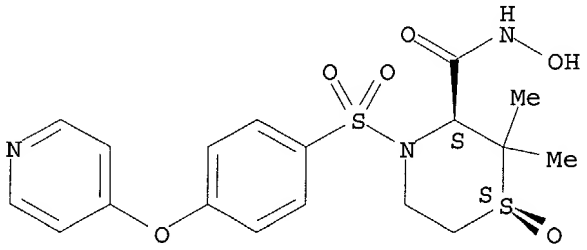
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



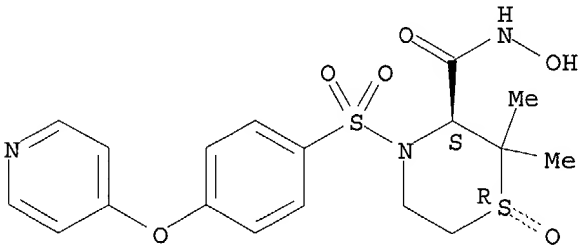
RN 192329-58-1 HCAPLUS
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1S,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 192330-53-3 HCAPLUS
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, 1-oxide, (1R,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 30 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
AB Matrix metalloproteinases are a family of zinc-contg. proteases that degrade extracellular matrix and basement membranes. These enzymes are thought to play a role in processes essential for **tumor** growth, invasion, and metastasis. Here the authors report pharmacokinetic and anti-**tumor** efficacy studies with a series of structurally related inhibitors of these enzymes that were synthesized at Agouron Pharmaceuticals using protein structure based drug design. The compds. studied were AG3287, AG3293, AG3294, AG3296, AG3319, and AG3340. Rat oral bioavailability ranged from 15 to 68%. Despite similar profiles of enzyme inhibition across the family of enzymes, and similar pharmacokinetics following i.p. administration to mice, efficacy against the Lewis **lung** carcinoma murine model varied from **tumor** growth

enhancement, to significant redns. in the size of primary **tumors** and the no. of **lung** metastases. AG3340 was the most efficacious compd. against the Lewis **lung** carcinoma model, resulting in the complete cessation of primary **tumor** growth throughout the expt. in 4/6 mice treated with daily i.p. injections at a dose of 50 mg/kg. This treatment inhibited the formation of **lung** metastases greater than 5 mm in diam. by 90%.

ACCESSION NUMBER: 1997:563763 HCAPLUS
DOCUMENT NUMBER: 127:214568
TITLE: Rodent pharmacokinetic and anti-tumor efficacy studies with a series of synthetic inhibitors of matrix metalloproteinases
AUTHOR(S): Santos, Orlando; Mcdermott, Charles D.; Daniels, Richard G.; Appelt, Krzysztof
CORPORATE SOURCE: Agouron Pharmaceuticals, Inc., San Diego, CA, USA
SOURCE: Clinical & Experimental Metastasis (1997), 15(5), 499-508
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB . . . proteases that degrade extracellular matrix and basement membranes. These enzymes are thought to play a role in processes essential for **tumor** growth, invasion, and metastasis. Here the authors report pharmacokinetic and anti-**tumor** efficacy studies with a series of structurally related inhibitors of these enzymes that were synthesized at Agouron Pharmaceuticals using protein. . . of enzyme inhibition across the family of enzymes, and similar pharmacokinetics following i.p. administration to mice, efficacy against the Lewis **lung** carcinoma murine model varied from **tumor** growth enhancement, to significant redns. in the size of primary **tumors** and the no. of **lung** metastases. AG3340 was the most efficacious compd. against the Lewis **lung** carcinoma model, resulting in the complete cessation of primary **tumor** growth throughout the expt. in 4/6 mice treated with daily i.p. injections at a dose of 50 mg/kg. This treatment inhibited the formation of **lung** metastases greater than 5 mm in diam. by 90%.

IT **Lung, neoplasm**
(carcinoma, Lewis; rodent pharmacokinetic and anti-**tumor** efficacy studies with series of synthetic inhibitors of matrix metalloproteinases)

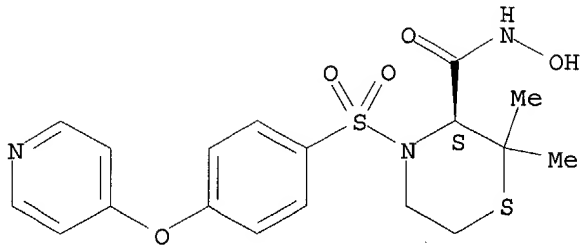
IT **192329-42-3**, AG 3340 195008-91-4, AG 3287 195008-92-5, AG 3293
195008-94-7, AG 3319 195008-95-8, AG 3296 195008-96-9, AG 3294
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(rodent pharmacokinetic and anti-tumor efficacy studies with series of synthetic inhibitors of matrix metalloproteinases)

IT **192329-42-3**, AG 3340
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(rodent pharmacokinetic and anti-tumor efficacy studies with series of synthetic inhibitors of matrix metalloproteinases)

RN 192329-42-3 HCAPLUS
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

09/857,876



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DELACROIX